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Editorial

By any other name

When pharmacology was a less fertile field, the names of drugs in current use provided no problem. Since all were old and established simple chemical or galenical preparations, the possibilities of drug designations were both limited and clearly delineated; there were the established Latin names and the established vulgar equivalents. The physician used the former, the common synonym was used only by the layman.

But progress, especially that of the recent past, has vastly complicated matters. There are so many really new drugs, so many veritable inventions of the chemist, that there has not been sufficient time for the natural development of a medical nomenclature, for a proper Latin name, to say nothing of an acceptable vulgar synonym. Since new names are essential if new drugs are to be used in commerce, and the laboratory device of using initials rarely suffices, name creation has developed simultaneously with drug invention.

Modern substitutes for the old system have been devised. Now we have the so-called generic name, which, if the drug comes to be recognized by the Council on Drugs or the U.S.P., may later be considered to be the official name, and we have the equivalent of the vulgar synonym, the trade name designed by the pharmaceutical manufacturer to help sell his drug. This given or proprietary name is his copyrighted property and is invariably prominently displayed. The former, which is public property, is placed in an inferior position on the label and usually in inferior type as well. Only a small, apparently exclusive, and perhaps peculiar, medical élite seems to use it.

Given names are properly selected by parents to provide a designation for their offspring which, in addition to being attractive, will help them get along in this world. It is just as natural that the progenitors of drugs should search assiduously for attractive names which will be an asset rather than a liability throughout the newborn drug's life. Since taste, purpose, background, and ambition all are considerations in these choices, it is understandable and acceptable that the standards of propriety and attractiveness should vary as much with pharmaceutical nominations as it does with those of individuals.

The coining of a suitable proprietary name, one which is effective, somehow suitable, and also in good taste, and the development of an appropriate generic

name, are by no means easy problems, and there is no intent here to belittle them. The danger of confusion with other drugs with similar names, especially if the latter are toxic or have undesirable properties, may be an important influence in shaping distinctive and even suggestive nomenclature. Where there is no chemical or pharmacologic connection between them, the attempt to avoid any implied association is certainly justified, even desirable as well as understandable. On the other hand, it is difficult to understand why a pharmaceutical manufacturer who has found a name for a product which presumably meets all these requirements for use in this country should find it necessary to invent another name for the same drug to use in another English-speaking country.

One can only advise that in all cases the fond parents use restraint and good taste in naming infants, and not be misled into thinking that the advantages of a good given name can be endlessly multiplied by the continuous extension of suggestive phrases even though it may violate good taste. Most ethical pharmaceutical manufacturers recognize this limitation to the potential of given names and are responsible for relatively few objectionable proprietary names. However, there are some highly suggestive proprietary names of new drugs which imply specific pharmacologic and therapeutic effects far too strongly. It must be emphasized that this sop to the lazy physician's tendency to avoid using his knowledge and his brain guarantees the implied virtues of the drug just about as little as does the name, Virginia, provide assurance of the bearer's chastity.

The so-called generic name has suffered badly at the hands of the name designers in recent times largely because this surname for drugs *should* have real meaning and too often does not. If the situation continues to develop along its present course, the piling up of ugly, meaningless, unpronounceable, unwieldy, and hard-to-memorize generic names cannot but result in the complete abandonment of their use by physicians.

If the generic name is to serve the same purpose as the family name, in addition to identifying the drug with a designation which is in the public domain and can therefore be applied to more than one brand of the same drug, it must communicate something of the family origins of the drug. A generic name should provide an easy clue to the genesis of the drugs, otherwise the term *generic* is a misnomer. The history of the naming of the barbituric acid derivatives is an especially good one and there are numerous examples of recent generic names which have provided information about the forbears of a drug, e.g., chlorothiazide and hydrochlorothiazide, but there are a few exceptions to this useful and meaningful system of nomenclature which lead one to suspect that sometimes so-called generic names inadvertently or deliberately hide a family skeleton.

One needs only to examine the generic names of new aminopyrine derivatives, of new skeletal muscle relaxants, of antihistamines, etc., for instances of strange new terms. Why is one drug baptized carisoprodol rather than isopropyl meprobamate? Consider that two congeners of amphetamine bear the generic names diethylpropion and phenylbutylamine. To one who is not well acquainted with the vagaries as well as the possibilities for variations on a single theme in chemical terminology, neither of these terms suggest any connection with the other or, for that matter, with amphetamine itself. How much more informative to have called them diethyloxyamphetamine and methylamphetamine! And since they are put to the same use as amphetamine, how much more appropriate! One can speculate why this was not done, but what is certainly a consequence of this verbal legerdemain is that the generic name sheds no light where the proprietary name also fails to illuminate, leaving the prescriber totally in the dark regarding the nature of his prescription.

Consider the so-called generic names

methandriol, diolostene, and mestenediol. Who is to be expected to know that although these also differ in proprietary names, all are really the same thing! And generic names change from time to time, further complicating matters even though the new names may be a simpler one, e.g., iron choline citrate chelate has just become ferro-cholinate. To be sure, such a change may seem like an actual improvement, but to the few who take the trouble to adopt a generic name when it comes out, such "improvements" are a source of annoyance, to those who would like to follow this course, a source of discouragement, and to those who do not care, a matter of no consequence. It is of obvious importance, therefore, to choose the best generic name at the outset.

Occasionally drug denominators do not stoop to discover a suitable generic name at all, completely avoiding the problem of creating an informative but relatively simple chemical designation, thereby giving the physician the choice between an easy proprietary name and a long, unsimplified, complete chemical formula. For example, one can ask for either α [α(-methyl-3, 4-methylenedioxyphenethylamino)-methyl] -protocetechuyl alcohol hydrochloride or a seven-letter proprietary equivalent for it. Since such a chemist's mouthful would probably stagger the memories as well as the verbal capacities and chemical aptitudes of most of our best practitioners, and it is also likely that it would have little meaning to most of our apothecaries, this practice seems to provide an impregnable method of forcing on the physician who wishes to use the drug the only remaining alternative, the proprietary name. Sometimes these chemical names are replaced by a more palatable generic name, but often only after the trade name has been irrevocably established by default.

One cannot argue the right of the pharmaceutical manufacturer to call his product what he thinks best for marketing it. But neither is the problem the same as that of creating names for new Pullman trains. It is also the ethical pharmaceutical manufacturer's obligation to the medical profession as well as to the public which pays for his product to label his drugs in a meaningful way, so that the physician can learn from a term on the label what he is actually giving his patient. Proprietary names which do not supply this information are acceptable only as long as the generic name provided serves this purpose. To fulfill this requirement, the generic name should not be confusing, it should not tax the memory, it should be tolerable to the physician who is not an expert chemist, it should be pronounceable, and it should be meaningful in that it should lead the physician to the source of the drug's action.

It is certainly the duty of the physician to find out what he is giving his patient for, if he is to practice effectively as well as safely with new drugs, he must know what the new agents really are and what their pharmacologic origins are. In this vast and rapidly growing field he often needs assistance. The nomenclature of new drugs should help him in this difficult task; a complex and completely uncorrelated nomenclature only makes matters more obscure and more difficult for him. Ultimately, this is bad for the patient. And what is bad for the patient ultimately dooms the drug.

Walter Modell

Commentary

Transposition of drug studies from laboratory to clinic

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A serious consideration of the transposition of drug studies from laboratory to clinical medicine implies that it is impractical for the pharmacologist to assess directly in man the value of many different compounds as potentially useful drugs. This is based on the following considerations: (1) the safety of the patient, (2) the lack of suitable large patient populations and (3) a sufficient number of astute clinical investigators, (4) the impracticality of synthesizing sufficient quantities of thousands of compounds, and (5) the sheer lack of enthusiasm for going through this effort for what would necessarily be a largely unfruitful search for useful therapeutic agents. The tremendous advancements in chemotherapy in recent years bear testimony to the ever-increasing success with which elegant drug research on laboratory animals can be transposed to man. The purpose of this editorial is to discuss some of the factors that determine success in this important, but poorly understood, area of research.

The comparative anatomy, physiology, and biochemistry of especially the higher vertebrates has been developed phylogenetically to accomplish the same general objectives of growth, maintenance, and reproduction. This has given rise to an admirable orderliness of function across a wide range of species. From such generalizations of individual functions has derived the laboratory approach to pharmacology and experimental therapeutics. The fact that the differentiation of species has evolved from common origins is responsible at once for both their over-all similarities and their immediate peculiarities. Thus, as we attempt to extrapolate the effect of a compound on a specific function in one animal to a similar function in another, we anticipate both the biochemical similarities and dissimilarities of the two, whether they be litter mates, or of different strains, classes, or even phyla.

Just as the similarities of organ functions among animals have made possible the laboratory science of pharmacology, the biochemical dissimilarities of species, of individuals, and even of tissues within the same animal have given stimulus to its recent advancement. Both the action and the elimination of a new compound must be determined by the existing metabolic makeup of the animal; therefore, the design of new therapeutic agents must conform as closely as possible to the physicochemical requisites for modulation of function. Setting aside for the moment the problem of safety, the compounds must avoid those characteristics that preclude effectiveness as by lack of absorption or by

rapid elimination. Thus, the successful transposition of results from the laboratory to the clinic presupposes that the characteristics that determine both action and elimination of that compound in other animals and man are not significantly different.

There are two basic principles that determine the likelihood of anticipating a successful extrapolation of results from laboratory animals to man or from experiments performed on animals to clinical therapeutic utility.[4] These are: (1) the more that is known about the performance of the compound under critically defined laboratory conditions, and (2) the closer the more elaborate laboratory experiments simulate the basic clinical conditions, the greater the likelihood that therapeutic utility can be predetermined. In other words, the more numerous and the more penetrating the questions that are asked at the laboratory stage, the less one has to guess and the more likely the clinical outlook can be predicted.

By themselves, in vitro testing results on a compound are apt to be misleading as an indication of clinical utility or, for that matter, efficacy in the experimental animal. Any number of examples can be cited to support this unreliability of predicting in vivo results from in vitro experiments. This is not to minimize the value of such data, but they should be viewed as an indication of the order or type of activity of a compound in a more or less rigidly defined system such as may obtain for in vitro enzyme studies and isolated organ studies. For example, the magnitude of inhibition of an in vitro sulfhydryl-catalyzed system such as succinic dehydrogenase bears no direct relationship to the diuretic potency of organomercurials, although it seems probable that the drugs act by influencing hydrogen ion transport secondary to some dehydrogenase inhibition. Likewise, the potency of chlorothiazide-like diuretics bears no quantitative relationship to their in vitro carbonic anhydrase inhibitory action even though they must possess this or what must be a very similar attribute to be effective. There is also the risk, as in the examples cited, that the in vitro system shown to be inhibited by a series of compounds does not bear a definitive relationship to their action in the whole animal. However, once a reasonable correlation is established between the activity of a general type of compound or functional group on a given in vitro system and the effect of such agents on a specific function in the whole animal, that single in vitro system may have served its purpose. Because in vitro systems are usually relatively simple, fast, and conservative of materials, they can be useful for screening large numbers of compounds for a single attribute; but since they may give no real indication of activity in vivo, their sole use prior to animal trials forfeits the possibility that still another type of compound may effect a desired action through a quite different mechanism.

The preceding discussion obtains as well for isolated tissue bath studies of the Magnus type. By working with isolated tracheal chains, perfused guinea pig lungs, or intestinal strips, one may note enormous differences in potency of antihistaminic agents, several of which, as it developed, have the same order of clinical dosage. Here again, these tests serve only to reveal interesting magnitudes of antihistaminic activity among these compounds. Actually, they bear only a superficial relationship to the fact that antihistaminic agents are most successfully employed to antagonize the vascular response to certain antigen-antibody reactions, such as can be simulated by histamine. They are not effective antispasmodic drugs for either the pulmonary or the intestinal system. Certainly such tests give no insight into the metabolic stability of other than the most labile compounds.

If one considers conjointly the principles of homeostasis and the integrative action of functional systems, it seems clear that the most definitive laboratory experiments should be designed to generalize the fundamental correlates of the clinical state to be influenced by a therapeutic agent.

Since the work of Ehrlich, the systematic advances in chemotherapy have required the development of suitable infections in laboratory animals by specific clinically important organisms. Such infections in animals generalize: (1) the many factors of host resistance to infection, and (2) the metabolic requisites to which a useful agent must conform, in addition to (3) the specific attribute it must possess.

The importance of sulfanilamide was appreciated not so much on the basis of in vitro antibacterial action, but in mouse infections that permitted the emergence of such critical factors as the role of host resistance, oral efficacy, and, later, the immense significance of correlating blood levels, based on the physiologic economy of the drug, with efficacy. To determine just the in vitro antibacterial action of a compound is to disregard the fact that an agent may increase significantly host resistance to experimental infection without being antibacterial itself. Analogously, the employment of probenecid as an adjunct to penicillin chemotherapy revealed that an agent that affected neither bacteria nor host resistance could enhance importantly the physiologic economy of the effective agent.[2]

If one can design into a highly generalized experiment a direct examination of the critical physiologic factor or factors that limit utility, it may be possible to set aside a superficial resemblance of the experiment to the clinical situation that characterizes the disease. Moreover, this can be done without a precise knowledge of either the etiology of the disease or the mode of action of the compound. In the foregoing sulfonamide example the mouse pneumococcal infection commonly employed is primarily a bacteremia rather than the pneumonia or meningitis the compounds so dramatically affected. Examination of the compounds that led to probenecid for their ability to inhibit the renal tubular secretion of penicillin provided a possible solution to a limiting factor in penicillin chemotherapy that had not been controlled before. Later it could be shown in the laboratory infection that probenecid reduced the ED_{50} dose for penicillin and the usefulness of the joint therapy was confirmed in the clinic. A more recent example is the experimental design from which chlorothiazide was selected. It was anticipated that a compound that would increase the excretion of sodium and chloride ions, in the manner of chlorothiazide, would be an effective diuretic agent and would be useful in the management of hypertension. Thus, the experimental design emphasized saluresis. Urine flow was all but disregarded in the short-term but fairly elaborate protocol in dogs, and no attempt was made prior to clinical trial to determine whether it would lower the blood pressure of hypertensive animals. Although chlorothiazide and its congeners can be picked up in today's rat diuretic assays which usually include the estimation of saluresis, it still would be difficult to demonstrate a convincing effect of the compound in laboratory hypertensive animals.

Research for drugs affecting mental health and illness seems handicapped for the very lack of physiologic correlates of disease and their measurement that have been established for the fields of infectious and cardiovascular-renal disease. The situation seems analogous to what might exist for chemotherapy if the etiological role of microorganisms were not yet recognized, or in the evaluation of antihypertension therapy if there were no means for measuring blood pressure. Even so, it is likely that the careful laboratory neuropharmacologic and neurophysiologic research and the equally careful clinical evaluation of new compounds will accelerate the development of this field of knowledge. There seems every reason to believe that the same generalizations regarding design of laboratory research and its transposition to the clinic that are mentioned herein for other categories of therapy will carry over to the broad field of mental illness.

There are other desirable features that

should be kept in mind regarding the design of experiments to establish utility: (1) Where possible, the more elaborate experiments should be capable of being audited at two or more points to determine reliability. Where applicable, the control phase should be designed into the protocol of a single experiment rather than being set up separately. Usually, renal clearance work, especially in dogs, is admirably adaptable to the employment of several variables and the results must be consistent if the experiment is to be considered reliable. Such experiments also lend themselves to a team approach where each member or group conducts a different portion of the experiment which is finally calculated and put together for interpretation. (2) The critical physiologic activity that a compound is being designed to influence should be approached by more than one type of experiment, where possible. This is especially pertinent to those areas where the physiologic correlates of the disease are not thoroughly understood. Such a situation would obtain for compounds that may be anticipated to be useful in allergy, but which are neither primarily antihistaminic agents nor adrenocorticoids. (3) It is preferable to extend the evaluation of a new compound to include more than one species, for the more uniform the response to a drug among several species, the more likely it is to be active in man. Conversely, if the order of activity of an agent varies markedly in several species, one should anticipate difficulty in extrapolating to clinical dosage. The curarimimetic agents are a most noteworthy example of the extreme variability of species response even to the point of production of flaccid paralysis by certain of these agents in some animals and of spastic paralysis in others.

The qualitative effect of a given agent on the body usually can be projected from laboratory animals to man reliably, if it is a fairly potent agent, but the effect of the body on the agent will frequently make the difference between a useful drug and a "near miss"—or a dud. Thus, it is not an uncommon experience for a compound to behave beautifully in small animals and to be worthless in man. Sometimes this can be anticipated by adequate studies on the fate of the drug in the laboratory animals.[6] Sometimes failure cannot be anticipated, but frequently it can be explained later by differences in rates of absorption, degradation, or excretion of the agent by the experimental animal and by man. Rather, the difficulty arises from the different adaptive metabolic processes that have evolved to accomplish the same over-all objectives in the various species. This biochemical individuality is discussed interestingly by Williams[5] in his book on the subject, in which many examples of species differences in the handling of drugs are documented.

Perhaps the most common fault is that a compound may not be as well absorbed following oral administration to man as was the case in the dog or smaller animals. It may not be possible to anticipate this unless there is considerable variation in the blood levels following oral administration of the compound to the two species. A compound may be adequately absorbed but, depending on its metabolic degradation or rate of excretion, the dosage for man may be higher or lower than what might have been anticipated from laboratory findings. Thus, the oral absorption of sulfamethazine by man, the dog, and the cow is excellent, and its renal clearance is very low. Even so, the compound is degraded rather rapidly by man so that its blood level curve falls fairly quickly. The fall in blood level is less rapid in the dog, and quite slow in the cow. On the other hand, the so-called biologic half-life of phenylbutazone is reported to be 3 hours in the rabbit, 6 hours in the dog, and 72 hours in man. Both carinamide and probenecid are inherently equally active in inhibiting penicillin excretion but they differ sufficiently in rates of conjugation and excretion that the effective dosage differs by tenfold in both dog and man. In man, the daily dosage for carinamide is

15 to 20 Gm., and 1.5 to 2 Gm. for probenecid.

The preclinical determination of differences in absorption, distribution, degradation, and excretion among compounds in series may be particularly useful in the election of one or more such agents for clinical trial. By employing a range of fairly elaborate tests for utility and by determining the metabolic disposition of an agent adequately, it has been possible to anticipate clinical usefulness and dosage with a good degree of reliability. The less adequately this is done, the less reliable has been the transposition from laboratory results to the clinic.

In general, the better the toxicity studies on a new compound, the greater assurance one has regarding its clinical safety. Usually, the order of acute toxicity determinations for laboratory animals bears little relationship to the toxicity of a compound for man except where toxicity is an extension of the overt pharmacodynamic effect of the agents, as for curarimimetic drugs or general anesthetics. The present trend of the subacute toxicity tests is to employ: (1) two or three species of animals, (2) a dosage range from no effect to lethal, and (3) a full complement of clinical, chemical, hematologic, and special studies, plus gross and histomorphic examinations. These results may make sober reading for the inexperienced clinical investigator, but they serve admirably when the full-scale chronic toxicity studies are being planned. Today higher dosages and more stringent circumstances are employed for toxicity studies than ever before, the intent being to induce toxicity almost regardless of the relevance of the toxic to the effective dosage. Such circumstances may be helpful or just confusing when the potential toxicity of a new agent is being evaluated. Thus, if a compound is so innocuous that the large amount necessarily added to the animals' diet to have an effect results in frank inanition, an impressive but irrelevant pathology report can be created. Likewise, it can be misleading to run a chronic toxicity test on an adrenocorticoid without employing unusual measures to counteract the reduced resistance of the animal to infection that attends the administration of massive dosages of the compound. Should a latent disease become active under these circumstances, the functional and cytopathologic changes can be difficult to assess. Clinical chemical tests that indicate impairment of function in the presence of histopathologic conditions may be altered pharmacodynamically by the action of very high dosages of a compound being studied. On the whole, the more stringent tests have helped to eliminate borderline compounds before they get to the clinic. The Pharmacology Section of the Food and Drug Administration can be most helpful in the design of relevant studies.[1]

It appears that the chronic toxicity study can serve little more than to assure that a compound is safe for extended clinical study. It is unreasonable to assume that even protracted studies on even a few hundred healthy pedigree animals can anticipate the vicissitudes that may befall a compound when administered to thousands or millions of patients with illnesses and complications of differing severity. Nor can one expect to foretell all the idiosyncratic responses of patients to drugs, some of which may even be psychogenic as judged by the discussions of the pharmacology of placebos by Wolf[7] and by Modell.[3]

The general experience of adequate carry-over of safety from carefully expanded toxicity studies in laboratory animals to man apparently has been good. The factor of *expanded* rather than *extended* studies should be emphasized. Whereas studies on drug distribution, metabolism, elimination, etc., employing the most sensitive methods have been most useful, the protracted extension of the duration of chronic toxicity studies has not added convincingly to the information that has been obtained.

In recent times it has dawned on the layman that he is not only beset by pathogenic microorganisms that he cannot see, but that

seemingly every inanimate substance and even his very hormones are carcinogenic. Today the pharmacologist is faced with the bewildering task of determining what is and what is not a carcinogen. Other characteristics pertaining to dosage-response, the relationship of frequency of administration to cumulative effect, and a seeming lack of reversibility of action have been considered in committee to follow more fatalistic generalizations than those to which we are accustomed. Until the basic principles applicable to drug-induced carcinogenesis are better understood, it is unlikely that really purposeful measures can be set up to detect weak carcinogens that may be present in or are unsuspectingly added to foodstuffs in minute amounts. Somehow superficial toxicity studies involving hundreds of animals and lasting for years are not a very reassuring measure for assessing at a preclinical level the potential carcinogenesis of an agent for man. This is an area where the reliability of transposition of drug studies from laboratory to clinic needs assiduous inquiry.

Summary

By employing a range of fairly elaborate tests for utility and by determining the metabolic disposition of an agent adequately, it has been possible to anticipate clinical usefulness and dosage with a good degree of reliability. The less adequately this is done, the less reliable has been the transposition from laboratory results to the clinic.

It would seem that the general experience of adequate carry-over of safety from careful, expanded toxicity studies in laboratory animals to man has been good. The factor of expanded rather than extended studies should be emphasized. Whereas studies on drug distribution, metabolism, elimination, etc., employing the most sensitive methods, have been most useful, the extension of the duration of chronic toxicity studies has not added convincingly to the information that has been obtained, at least to date.

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Effect of certain drugs on the incidence of seasickness

Several drugs were tested, some of them for the first time, against seasickness in military personnel on transport ships on the North Atlantic ocean. All of the drugs were given three times a day. Of the new ones tested phenglutarmide, 2.5 mg., and cinnarazine, 7.5 mg., were significantly effective on a single trip. Somewhat less effective were atropine and orphenadrine.

Ineffective new drugs were procyclidine, diethazine, cycrimine, caramiphen, pheniprazine, nialamide, phenelzine, benactyzine, and promazine.

Cyclizine and meclizine, in doses of 50 mg. three times a day, were again found to be effective.

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During the past several years the Army, Navy, and Air Force have cooperated in evaluating the effectiveness of a number of drugs for the prophylaxis of seasickness in volunteer troops on board military transport ships from New York to Bremerhaven, Germany, and return.[1] The results of the tests of more than 60 drugs in nearly 24,000 subjects have shown that some parasympatholytic drugs, such as scopolamine, certain antihistaminic drugs, such as diphenhydramine and promethazine, and other drugs that are piperazine derivatives, such as cyclizine and meclizine, all are effective in reducing significantly the incidence of seasickness. Many earlier studies on drugs in motion sickness are summarized in a recent review.[4]

The manner in which drugs protect against motion sickness is poorly understood. They may act upon the receptors of the vestibular system, the afferent nerves of this system, or possibly by depressing the emetic center, but the evidence is not convincing. It seems probable that they

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It is evident that this operational study, involving so many troops and the preparation of so many drugs, required the support of many individuals and offices. The Committee on Motion Sickness is especially grateful for the efforts of Dr. Howard Karsner, the Offices of the Surgeons General of the Army and Navy, Chief of Transportation, U.S. Army, every level of the Military Sea Transport Service command, personnel at Fort Riley, Kan., and Camp Dix, N. J., and members of the 16th and 18th Infantry Divisions, U.S. Army.

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may antagonize centrally the effects of such chemical substances as acetylcholine. Thus a number of hypotheses still require study. The drugs for this series of trips were selected to answer some of these.

The demonstration that certain drugs are capable of inhibiting the metabolism of serotonin and norepinephrine in the brain[2] suggested that substances such as monoamine oxidase inhibitors should increase the incidence of motion sickness if the condition were associated with the accumulation of naturally occurring amines. To test this hypothesis pheniprazine (Catron), phenelzine (Nardil), and nialazide (Niamid) were chosen for study.

Among the first drugs found to be moderately effective against motion sickness were scopolamine and atropine. Repeated tests have demonstrated the effectiveness of scopolamine[5,7,8,9] but atropine has been studied less frequently. Both of these drugs are used in the therapy of Parkinson's disease and a number of synthetic substitutes for these have been shown to be effective in motion sickness. For this reason phenglutarmide (Aturban), diethazine (Diparcol), orphenadrine (Disipal), procyclidine (Kemadrin), cycrimine (Pagitane), and caramiphen (Panparnit) were chosen for study. Benactyzine, a tranquilizing drug, has considerable anticholinergic activity and was selected for this reason.

Earlier studies had demonstrated that chlorpromazine was relatively ineffective in seasickness[6] whereas a related compound, promethazine, was effective,[3] so it was of interest to determine whether the related nonhalogenated promazine would have demonstrable activity.

Since meclizine (Bonine) has consistently demonstrated its effectiveness in seasickness[1,3] it was of interest to test the closely related compound cinnarazine (Mitronal).

While earlier tests had demonstrated the effectiveness of cyclizine and meclizine in doses of 50 mg., usually given three times a day, smaller and larger doses of these drugs previously had not been tested, so some dosage response evaluations were scheduled.

Procedures and results

The experimental procedures were much the same as those previously employed.[1] Volunteer male service personnel being transported from New York to Bremerhaven, Germany, on Military Sea Transport Service ships of the P-2 type served as subjects. After a preliminary briefing each man was given a test card. This card contained spaces for pertinent data such as the name, age, weight, and height of the subject and a place to record symptoms and possible drug side effects which might be experienced after taking the drug. The card also contained code systems to indicate the medication used and the number of doses given.

All drugs were mixed with lactose and placed in No. 1 pink gelatin capsules. The first dose was given prior to the evening meal either just before or after leaving port. Subsequently, subjects received a capsule before each meal for a total of nine capsules.*

After the experiment each subject completed the questionnaire card and was interviewed briefly to insure obtaining as much data as possible, especially to establish the time vomiting may have occurred.

The number of subjects who received the various drugs for the specified period

*The drugs that were used were supplied as follows: benactyzine hydrochloride as Suavitil by Merck Sharp & Dohme, West Point, Pa.; caramiphen hydrochloride as Panparnit by Geigy Co., Inc., New York 13, N.Y; cinnarazine hydrochloride as Mitronal hydrochloride by G. D. Searle & Co., Chicago, Ill.; cyclizine hydrochloride as Marezine hydrochloride and procyclidine hydrochloride as Kemadrin by Burroughs Wellcome & Co., Inc., Tuckahoe, N.Y.; cycrimine hydrochloride as Pagitane hydrochloride by Eli Lilly and Company, Indianapolis, Ind.; diethazine hydrochloride as Diparcol by Rhone-Poulenc, Paris, France; phenglutarmide as Aturban by Ciba Pharmaceutical Products, Inc., Summit, N.J.; meclizine hydrochloride as Bonamine hydrochloride and nialamide as Niamid by Chas. Pfizer & Co., Inc., Brooklyn, N.Y.; orphenadrine hydrochloride as Disipal by Riker Laboratories, Inc., Northridge, Calif.; pheniprazine as Catron by Lakeside Laboratories, Inc., Milwaukee, Wis.; phenelzine as Nardil by Warner-Chilcott Laboratories, Morris Plains, N.J.; and promazine hydrochloride as Sparine hydrochloride by Wyeth Institute for Medical Research, Philadelphia, Pa.

Table I. *Effectiveness of various drugs against seasickness*

Compound	Dose (mg.)	First trip				Second trip				Third trip			
		No. of subjects	Vomiting			No. of subjects	Vomiting			No. of subjects	Vomiting		
			No.	%	SL*		No.	%	SL*		No.	%	SL*
Placebo		82	7	8.5	—	122	27	22.1	—	71	12	16.9	—
Atropine sulfate	1.0	94	4	4.2	.30								
Benactyzine	3									61	8	13.1	.50
Caramiphen HCl	50	86	6	7.0	.80								
Cinnarazine	7.5					148	14	9.4	.02	73	9	12.3	.50
Cinnarazine	15.0					138	20	14.5	.20				
Cyclizine	25									66	5	7.6	.20
Cyclizine	50									69	0	0.0	.001
Cyclizine	100									71	11	15.5	.90
Cycrimine HCl	2.5	85	6	7.1	.70								
Diethazine HCl	250	83	6	7.2	.80								
2-(2-Diethylamino-ethyl)-2-phenyl-glutarimide	2.5	93	2	2.2	.05								
Meclizine HCl	12.5									68	8	11.8	.50
Meclizine HCl	25									80	11	13.8	.50
Meclizine HCl	50	97	1	1.0	.05	137	11	8.1	.01	76	9	11.8	.50
Meclizine HCl	100	84	6	7.1	.80								
Nialamide	20					127	25	19.7	.80				
Orphenadrine HCl	50	94	3	3.2	.20								
Phenelzine hydrogen sulfate	25					123	36	29.3	.50				
Pheniprazine	6.25					122	28	22.9	.95				
Pheniprazine	12.5					127	36	28.3	.50				
Procyclidine HCl	2.5	97	7	7.2	.80								
Promazine	50									67	11	16.4	.95

*Significant level of difference from placebo group.

of time and the incidence of vomiting are recorded in Table I. The percentage incidence of vomiting for each drug-dosage was compared with the percentage incidence of vomiting under placebos. The results of the first trip show that only meclizine, in a dose of 50 mg., and phenglutarmide were effective at the 5 per cent level ($p=0.05$). There was some evidence that meclizine in 100 mg. doses, which are larger

than those recommended, was less effective than in the usual dose of 50 mg. In interpreting the data from this trip it will be noted that the incidence of vomiting in the placebo group was only 8.5 per cent. This may mean that two of the drugs, atropine and orphenadrine, associated with a low incidence of vomiting on this trip, might well have exhibited significant protection in a larger series or on a rougher trip.

On the second trip meclizine in doses of 50 mg. was highly effective ($p = 0.01$) and cinnarazine in a dose of 7.5 mg. also was effective ($p = 0.02$). On the third trip cyclizine, at the usually recommended dose of 50 mg., prevented vomiting in all subjects and was highly effective ($p = 0.001$).

The failure to demonstrate that a number of drugs gave significant protection on a single trip should not be accepted as sufficient evidence that they may not be effective under other circumstances. In a larger study with 15 trips[1] several drugs known to be effective gave results on one single trip which were no different from results obtained with placebos. In this study similar puzzling results were obtained for both meclizine and cyclizine. On the third trip (Table I), meclizine in each of the dosages gave results no different from those of the placebos. Again the failure to obtain protection with doses of 100 mg. meclizine or cyclizine was an unexpected result, which remains unexplained except in terms of some uniqueness of that particular ocean passage.

Under the condition of these experiments it was difficult to estimate the true incidence of side effects due to the drugs. The symptoms associated with nausea and vomiting often obscured drug-induced effects. Thus, neglecting the specific medication, the subjects who vomited were, on the average, more likely to experience dizziness, nervousness, sweating, dry mouth, weakness, tiredness, [illegible] nia, dreams, tingling, diarrhea, and ringing in the ears than subjects who did not vomit.

There was some evidence that subjects who received caramiphen or cycrimine were more likely to experience dizziness. Blurred vision occurred more frequently after atropine, phenglutarmide, cycrimine, orphenadrine, and caramiphen. A feeling of dry mouth was experienced more frequently after atropine, cycrimine, caramiphen, and nialamide. None of the drugs produced significant increases in the incidence of drowsiness, insomnia, gastrointestinal disturbances, or skin irritation.

Not one of the drugs believed to inhibit amine oxidase in the central nervous system was any more effective in protecting from motion sickness than the placebos.

Neither did they increase significantly the incidence of vomiting. Thus the data presented here offer no support for the hypothesis that the vomiting of motion sickness may be a consequence of increased concentrations of biogenic amines.

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Abnormal symptoms, signs, and laboratory tests during treatment with phenothiazine derivatives

Complications were neither frequent nor severe in 599 newly admitted schizophrenic patients treated for 12 weeks with chlorpromazine, trifluprομazine, mepazine, prochlorperazine, perphenazine, and phenobarbital. Twelve patients were dropped from treatment because of adverse symptoms or signs, 5 because of hematologic abnormalities, and 4 because of deviant hepatic tests.

Many abnormal symptoms and signs generally thought to be associated with phenothiazine drug therapy also occurred during treatment with phenobarbital. Leucopenia was not significantly more frequent from phenothiazines than from phenobarbital. No significant differences in abnormal hepatic tests were noted between the 6 agents. Most abnormal tests were isolated and sporadic. No frank case of intrahepatic obstructive jaundice was observed. Changes in body temperature, pulse rate, and blood pressure were uncommon, with no significant differences in frequency between the drug regimens.

Not all abnormalities in symptoms, signs, and laboratory tests which occurred during treatment can be attributed to it. At least some must be spontaneous fluctuations in the population studied.

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Wide experience with the phenothiazine derivatives in clinical use has delineated the prevalence of undesirable effects or abnormal laboratory tests, as they are studied under varied conditions. A controlled study by the Veterans Administration suggests that the incidence of reactions and abnormal laboratory findings may be smaller than is generally believed, and these must be evaluated against a background of behavioral, hematologic, hepatic, and autonomic nervous system variability inherent in a schizophrenic population.

Six drugs (chlorpromazine, trifluprομazine, mepazine, prochlorperazine, perphenazine, and phenobarbital) were given for a 12 week period to 599 newly admitted

Staff from 35 hospitals participating in Project No. 3, Veterans Administration Cooperative Studies in Chemotherapy in Psychiatry, collected the data used for this study.

schizophrenic men in 35 Veterans Administration Hospitals.[1] A double blind control was employed, using "equivalent" doses of each of the 6 agents in both an initially determined and later flexible dosage schedule. Biasing factors were that the sample was composed of men under the age of 51 years, some of whom had previously received phenothiazine derivatives. Except for their mental illness, the patients were generally in good health.

Methods of study

Four specific types of information were sought: (1) the prevalence of clinical symptoms or signs frequently reported as occurring with phenothiazine derivatives[2,5,7,11]; (2) the prevalence of abnormalities in hematologic measures, especially total leukocyte count, absolute neutrophil count, and eosinophil count; (3) the prevalence of positive hepatic findings; (4) the occurrence of aberrations in body temperature, pulse rate, or blood pressure.

A symptom-sign check list for each of 14 specific items was completed weekly by the attending physician on each patient. Thus information was obtained about the prevalence, the time of onset, and the duration of each of these manifestations.

Total and differential leukocyte counts were obtained on each patient prior to and during each of the 12 weeks of treatment. If other hematologic tests were deemed necessary, these were obtained at the discretion of the attending physician. For purposes of this study leukocytosis was considered to be present if the total leukocyte count exceeded 13,500 per cubic milliliter. No lower limit was imposed on the total leukocyte count for determining the presence of leukopenia; rather this was deemed to be more accurately represented by a calculation of the absolute neutrophil count (total leukocyte count times per cent of neutrophils). An absolute neutrophil count of 3,000 per cubic milliliter was considered as the lower limit of normal. A patient was regarded as leukopenic when the absolute neutrophil count dropped below 1,800. Absolute neutrophil counts of less than 1,500 per cubic milliliter were considered to represent a potentially dangerous situation, but the decision as to whether or not treatment should be continued was left to the attending physician. Eosinophil counts of 7 per cent or more were considered to be elevated. All these data were tabulated on an appropriate form for each of the 12 weeks of treatment.

The study protocol also recommended that each patient have hepatic tests performed prior to and during the first 5 weeks of treatment. Recommended as preferential screening hepatic tests were the alkaline phosphatase determination and the serum glutamic oxalacetic acid transaminase (SGO-T) test. If either of these tests was abnormal (over 8 Bodansky units for the alkaline phosphatase test and over 40 units for the SGO-T test), other hepatic tests were to be performed. These included determinations of the total serum bilirubin, cephalin flocculation, and Bromsulphalein (BSP) retention. The upper limits of normal were set at 1.2 mg. per 100 ml., 3+ at 48 hours, and more than 8 per cent retention, respectively, for each of the tests.

Each participating hospital was requested to make daily measures of patients' temperatures during the entire treatment course and daily measures of blood pressure and resting pulse rates during the first week of treatment. Naturally, great variations occurred in conditions under which these measures were made in various patients.

Results of study

Control values for total neutrophil count, alkaline phosphatase and SGO-T determinations. Data on the total leukocyte count of 475 patients prior to treatment were tabulated. The mean control leukocyte count was 8,200 per cubic milliliter with a standard deviation of 2,750. Ninety-seven patients (more than 20 per cent) had control total leukocyte counts of over 10,000 per cubic milliliter. In 80 of these 97 patients the total leukocyte count

Table I. *Comparison* between drugs in occurrence of clinically noted side effects during 12 week treatment period*

Perphenazine	Produced *more* drowsiness and extrapyramidal effects (impaired associated movements, rigidity, tremor, and akathisia) than *phenobarbital* or *mepazine*; *more* extrapyramidal effects (rigidity, tremor, and akathisia) than *trifluprομazine*; *more* extrapyramidal effects (impaired associated movements, rigidity, and akathisia) than chlorpromazine; and *more* akathisia than *prochlorperazine.*
Prochlorperazine	Produced *more* drowsiness, extrapyramidal effects (impaired associated movements, rigidity, tremor, akathisia) and nausea or vomiting than *phenobarbital*; *more* drowsiness, extrapyramidal effects (impaired associated movements, rigidity), weakness or fatigue, and nausea or vomiting than *mepazine.*
Chlorpromazine	Produced *more* drowsiness, extrapyramidal effects (rigidity, tremor) than *phenobarbital*; *more* drowsiness, impaired associated movements, and weakness or fatigue than *mepazine.*
Trifluprομazine	Produced *more* extrapyramidal effects (impaired associated movements) than *phenobarbital*; *more* impaired associated movements than *mepazine. Complete absence of side effects was more common* than with *prochlorperazine* or *perphenazine.*
Mepazine	Produced *more* blurred vision than *phenobarbital* or *trifluprομazine.*
Phenobarbital	Produced *more* excitement and agitation than *mepazine, trifluprομazine, chlorpromazine,* or *prochlorperazine. Complete absence of side effects* was *more common* than with *prochlorperazine* or *perphenazine.*

*Only differences significant at the 5 per cent level using chi square comparisons of the drug pairs are stated.

was in the 10,000 to 13,500 range, in 11 between 13,500 and 16,000, and in 6 over 16,000 per cubic milliliter. The maximum control leukocyte count observed was 22,500 per cubic milliliter. Nineteen patients had control leukocyte counts of less than 5,000 and only 3 of these 19 patients had total leukocyte counts of less than 4,000 per cubic milliliter. Thus leukocytosis by ordinary standards was comparatively common in this schizophrenic population but leukopenia was neither frequent nor severe.

Determination of control values for alkaline phosphatase was more complicated because they were reported in 4 different kinds of units. The largest sample consisted of reports in Bodansky units which were available on 256 patients. The mean value in Bodansky units for control alkaline phosphatase determinations was 4 units with a standard deviation of 1.8 units. Six patients had control values for alkaline phosphatase greater than 8 units.

SGO-T determinations were performed on 154 patients. The mean value for this determination was 24.8 units with a standard deviation of 19.4 units. Nineteen patients showed control elevations of SGO-T titer to more than 40 units.

Abnormal signs and symptoms. Data on the occurrence of abnormal symptoms and signs were available for the entire sample of 599 patients. Twelve patients were dropped from treatment because of side reactions. No abnormal symptoms or signs were reported in 167 patients. These 167 patients were not distributed among the 6 treatment groups as might have been expected by chance, so each drug group was compared individually with every other drug group and tested for significance by the chi square test. Each symptom or sign was evaluated in the same manner. If a patient was reported as manifesting a particular symptom at any time during the study period, he was tallied once regardless of whether the symptom occurred during one or more weeks. When a significant difference among the 6 groups was observed for any symptom, the groups were then compared by pairs. Ten symptoms showed significant differences between the treatment groups.

Table I compares the drugs with regard to clinical evidence of side effects during the 12 week treatment period. Perphenazine and prochlorperazine, both piperazine derivatives, produced more reactions than

the other drug. The two aliphatic derivatives, chlorpromazine and trifluprom azine, produced more reactions than the piperidine derivative, mepazine, or phenobarbital.

Table II indicates the number of patients showing any abnormal symptom in each of the drug treatment groups. The median daily dose at which drowsiness was produced varied considerably (prochlorperazine, 35 mg.; perphenazine, 48 mg.; trifluprom azine, 60 mg.; mepazine, 75 mg.; phenobarbital, 96 mg.; chlorpromazine, 200 mg.). The majority of adverse behavioral effects appeared during the first 3 weeks of treatment; their persistence was comparable for each of the drugs. Mental depression and "turbulence" (anxiety and agitation), usually considered adverse effects of phenothiazine derivatives, were equally common with phenobarbital.

Extrapyramidal effects were more frequent from the piperazinylphenothiazines

Table II. *Number of patients in each drug group showing clinically observed side effects*

Symptom or sign	*Total N = 599*	*Phenobarbital 99*	*Prochlorperazine 100*	*Trifluprom azine 96*	*Mepazine 103*	*Prochlorperazine 100*	*Perphenazine 101*
Adverse behavior							
Drowsiness	232	28	48	38	28	44	46
Depression	103	18	15	13	15	23	19
Anxiety	198	38	29	26	28	41	36
Agitation	181	44	20	26	30	27	34
Central nervous system							
Extrapyramidal effects	52	0	8	6	2	15	21
Impaired associated movements	57	2	8	10	1	16	20
Rigidity	62	0	9	9	2	15	27
Tremor	47	2	10	5	5	10	15
Akathisia	110	12	16	16	12	20	34
Dystonia (spasm)	16	1	2	3	1	3	6
Weakness, fatigue	135	16	28	18	16	29	28
Seizures	4	0	0	1	1	1	1
Autonomic nervous system							
Fainting	16	2	4	1	2	4	3
Blurred vision	90	10	16	8	24	14	18
Nausea, vomiting	60	6	13	10	5	17	9
Dryness of mouth	107	13	20	11	24	20	19
Constipation	89	10	17	14	23	12	13
Allergic effects							
Dermatitis	21	3	7	4	2	4	1

Table III. *Changes in leukocyte and eosinophil counts during 12 week treatment period*

Drug	*Eosinophilia*		*Leukocytosis*		*Leukopenia*	
	No. of patients	*Total No. counts*	*No. of patients*	*Total No. counts*	*No. of patients*	*Total No. counts*
Phenobarbital	20 (4)*	40	16 (3)	40	9 (5)	19
Chlorpromazine	18 (3)	34	12 (2)	13	7 (6)	23
Trifluprom azine	11 (0)	22	11 (3)	32	3 (3)	4
Mepazine	17 (4)	37	12 (4)	25	8 (5)	29
Prochlorperazine	16 (1)	42	19 (1)	42	2 (3)	5
Perphenazine	16 (4)	31	16 (2)	33	7 (4)	14

*Numbers in parentheses indicate patients with abnormal control values.

than the others. As might be expected, no patient treated with phenobarbital was believed to have the complete extrapyramidal syndrome. These effects were most frequent in the third week of treatment, at daily doses of 48 mg. of perphenazine, 75 mg. of prochlorperazine, 150 mg. of trifluprom azine, and 600 mg. of chlorpromazine. Patients receiving phenobarbital reported as having akathisia probably reflected the difficulty in distinguishing this symptom-complex from the ordinary manifestations of psychosis. Similarly, an instance of dystonic syndrome with phenobarbital must have reflected an error in clinical judgment, as this syndrome is unique for phenothiazine derivatives.

As extrapyramidal syndromes are frequently said to correlate with clinical improvement, such a relationship was sought in the case of perphenazine and prochlorperazine. Substantial clinical improvement was arbitrarily defined as a reduction of 25 per cent or more from the initial total morbidity score (measured by the Multidimensional Scale for Rating Psychiatric Patients) at the end of 12 weeks of treatment. Any change less than this was considered insufficient improvement. These two categories of improvement were then grouped according to the presence or absence of extrapyramidal syndromes. No statistically significant differences were noted between groups showing substantial improvement and those not, either with or without extrapyramidal effects, in the case of either drug.

Although autonomic nervous system effects are not related to the pharmacologic action of phenobarbital, a surprising number were recorded. Presumably these represent normal variations in the state of the patients, rather than drug effects. They tended to occur later in the course than with the phenothiazine derivatives, which usually produced these effects immediately and at low doses.

Cases of dermatitis were too few to show much distinction between the drugs. The occurrence of this complication with phenobarbital was not surprising as allergic eruptions with barbiturates should be expected.

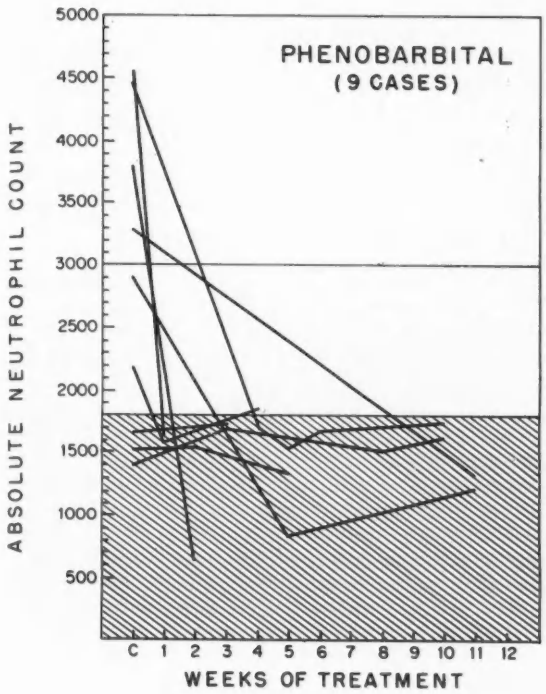
Changes in leukocyte and eosinophil counts. The occurrence of eosinophilia, leukocytosis, and leukopenia is shown in Table III. None of the differences between drug groups were statistically significant.

Eosinophilia was most frequently noted, being highest for phenobarbital (even when corrected for 2 abnormally elevated counts in the control period) and lowest with trifluprom azine. The total number of

Table IV. *Occurrence of abnormal hepatic tests during 12 week treatment period*

Drug	*Patients with abnormal tests*	*No. with 2 or more abnormal tests*	*Total serum bilirubin over 1.2 mg. %*	*SGO-T titer over 40 units*	*Alkaline phosphatase over 8 units (Bodansky)*	*Cephalin flocculation 3 plus or more in 48 hours*	*BSP retention over 8 per cent in 45 minutes*
Phenobarbital	20 (10)*	6 (5)	4	10	4	6	3
Chlorpromazine	19 (5)	3 (1)	4	9	5	5	0
Trifluprom azine	11 (2)	6 (2)	2	10	4	3	0
Mepazine	16 (8)	5 (3)	6	9	3	3	1
Prochlorperazine	17 (4)	3 (1)	0	11	6	1	2
Perphenazine	14 (7)	3 (1)	2	9	2	3	1
Total	97 (36)	26 (13)					
		Range of values	1.3-2.7 mg. per 101 ml.	40-177 units	8.2-14 units	3-4 plus	9-17%

*Numbers in parentheses indicate patients with abnormal control values.



Figs. 1 to 5. Course of absolute neutrophil counts in patients who developed leukopenia during treatment with five phenothiazine derivatives and phenobarbital. (After initial count, only counts in leukopenic range are shown, preceding or succeeding counts being above the leukopenic level.)

abnormal counts paralleled the number of patients showing such abnormalities. The degree of eosinophilia was comparable among various treatment groups, generally being mild. In 77 per cent of patients, counts were below 10 per cent. Although eosinophil counts as high as 20 per cent were observed, these were comparatively rare, only 17 counts of 13 per cent or more being observed. The frequency of abnormal eosinophil counts was rather evenly distributed through the 12 weeks of treatment and the control week.

The next most common hematologic abnormality was leukocytosis. The total number of elevated counts paralleled the distribution of patients with leukocytosis. Elevated counts were evenly distributed throughout the 12 weeks of treatment and the control week. The degree of leukocytosis observed was surprisingly high; over one-half the counts exceeded 15,000 per cubic milliliter, the median range being 15,000 to 16,500.

Leukopenia was comparatively infrequent in this group. Of 36 patients with leukopenia 5 were dropped from treatment. This abnormality was observed most frequently in patients treated with phenobarbital and least frequently in patients treated with prochlorperazine and trifluprom azine. The course of leukopenic counts in such patients is shown in Figs. 1 through 5. Although the absolute neutrophil count decreased to less than 1,500 per cubic milliliter with each of the 6 drugs, in those cases in which treatment was continued without interruption, counts subsequently returned to higher levels.

Abnormal hepatic tests. Abnormal hepatic tests occurred in 97 patients without statistically significant differences between the treatment groups (Table IV). In 36 of these 97 patients abnormal tests were present during the control period. Only 26 patients had more than a single abnormal test during the 5 week period of measure-

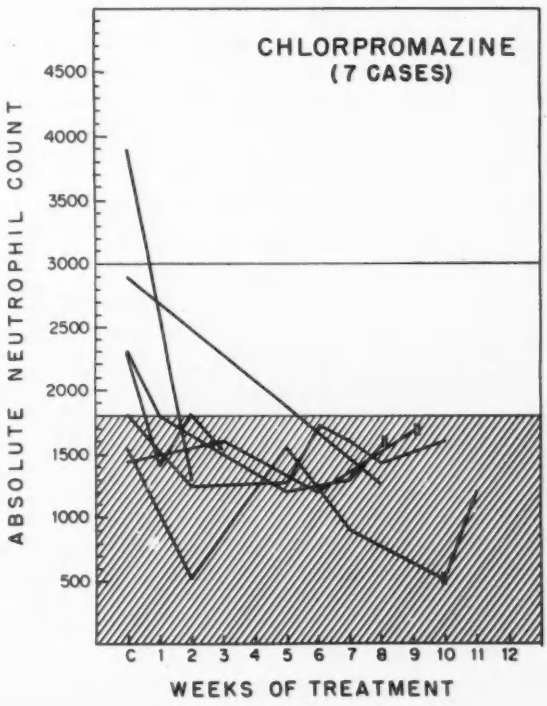


Fig. 2.

ment. Most abnormalities were found in the SGO-T titer, alkaline phosphatase determinations, and serum bilirubin levels. However, these tests were performed most frequently. As can be seen from the table, the range of abnormal values was not great, few tests being at the upper limits.

Interpretation of such abnormal tests, occurring sporadically and infrequently, was extremely difficult. In no instance was there a distinguishing pattern of persistent abnormal tests as occurs ordinarily in hepatic dysfunction following administration of phenothiazine derivatives. Prodromal symptoms or the appearance of clinical jaundice was not reported in any patient. Four patients were dropped from treatment because of abnormal hepatic tests without other abnormal clinical signs or laboratory findings. One patient treated with perphenazine had several abnormal control tests with persisting abnormalities through the early part of his treatment period. These tests were only mildly erratic but indicated pre-existing parenchymatous liver damage which was not aggravated by drug therapy.

Changes in temperature, pulse, and blood pressure. Temperatures which changed significantly were lower. Only oral temperatures of less than 97° F. were considered abnormally low (Table V). The distribution of this type of abnormal body temperature varied between the treatment groups. A few patients in each treatment group showed persistently low body temperatures ranging between 95° and 97° F. The frequency and persistence of these low temperatures throughout treatment (and often through the control period) suggested that these individuals had low body temperatures normally. In other instances the lowering of body temperatures was sporadic. No single sharp elevations of temperature occurred such as have occasionally been reported with phenothiazine derivatives, nor was any sustained elevation of temperature reported.

Table V. *Changes in temperature, pulse rate, and blood pressure during 12 week treatment period*

Drug	*Temperature less than 97° F.*	*Pulse rate over 110 per minute*	*Blood pressure decline: 30 mm. systolic and/or 20 mm. diastolic*
Phenobarbital	8	0	3
Chlorpromazine	7	1	5
Trifluprom azine	8	1	2
Mepazine	12	2	2
Prochlorperazine	8	1	8
Perphenazine	7	1	5

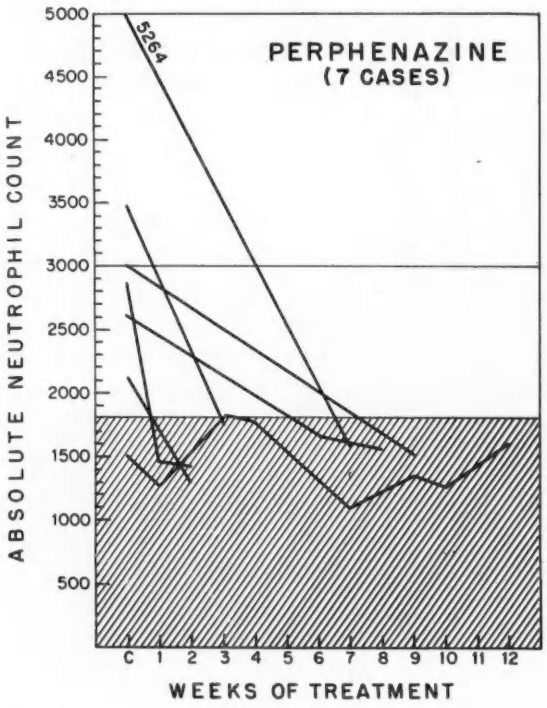


Fig. 3.

Changes in pulse rate were surprisingly rare. Patients who had tachycardia did not have it persistently, only occasionally. On the other hand, in a number of cases pulse rates declined under drug treatment, perhaps because of some abatement of anxiety.

Changes in blood pressure were uncommon. In practically all cases the blood pressure never fell below the usual physiologic limits. The usual pattern was a fall from an initially elevated or borderline level of blood pressure to a physiologic level either in the middle range or at the low side. The

varying conditions under which these measurements were obtained detract from their significance.

Discussion

Well-controlled studies for determining abnormal symptoms, signs, and laboratory tests associated with drug therapy take spontaneous occurrence into account and tend to eliminate the biasing factor of clinical expectation. The disadvantages of our technique are that the ranges of drug dosage are arbitrary during the critical early part of therapy and that the technique of observation of patients varies greatly. The dosage schedule in this study was therapeutically efficacious, simulating usual clinical conditions. Differences between observers should have been equally distributed among the 6 treatment groups, not constituting a major biasing factor.

Consideration of the occurrence of abnormal signs and symptoms in the 6 treatment groups led to three possible conclusions: (1) Their occurrence with phenothiazine derivatives has been greatly overestimated. (2) Phenobarbital produces more side effects than is ordinarily believed. (3) Many phenomena represent spontaneous fluctuations in schizophrenic patients or manifestations of the illness itself. Of these, the last has probably not been stressed enough. Examples of the first possibility were the relatively infrequent occurrence of extrapyramidal syndromes (less than 10 per cent), seizures, and skin eruptions in patients treated with phenothiazine derivatives. Examples of the second and third possibilities were the occurrence of depression, anxiety, agitation, akathisia, and autonomic nervous system side effects during therapy with phenobarbital. The abnormal behavioral symptoms were probably manifestations of schizophrenia rather than drug effects.

Leukocytosis, leukopenia, and eosinophilia are known to be consequences of treatment with phenothiazine derivatives.[3,8,12] However, each hematologic abnormality was present in control counts and just as frequent during treatment with phenobarbital as with the other drugs. The development of leukopenia during drug therapy is especially important. Twenty-five of the 36 patients in this study with leukopenia (absolute neutrophil counts

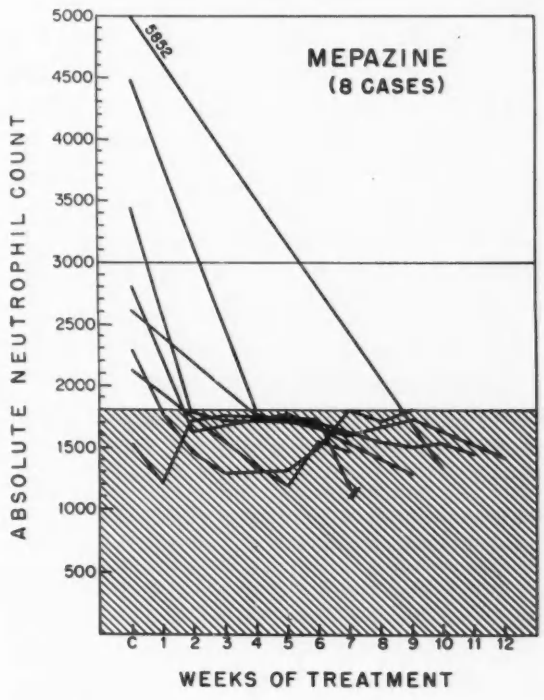


Fig. 4.

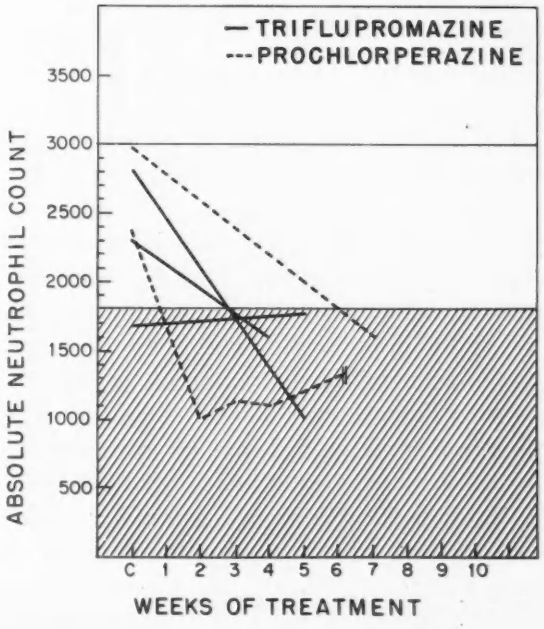


Fig. 5.

below 1,800 per cubic milliliter) had absolute neutrophil counts of less than 3,000 per cubic milliliter during the week preceding treatment. This suggests that patients beginning with low neutrophil counts are more prone to further depression during treatment. On the other hand, leukopenia from phenothiazine derivatives was not significantly more frequent than that from phenobarbital. Still more remarkable was the return to normal levels of considerably depressed absolute neutrophil counts despite uninterrupted treatment. Continuation of treatment did not produce agranulocytosis, but was succeeded eventually by normal counts. Obviously, the decision to continue or abandon treatment in the face of leukopenia must be made on more factors than a declining leukocyte count. In view of the occurrence of leukopenia with phenobarbital, it may be assumed that some patients may have spontaneously occurring cyclic leukopenia unrelated to drugs.

Abnormal hepatic tests were common in all treatment groups. More than one-third of patients with abnormal tests had them during the control period. More significant was the fact that no patient developed a clinical or laboratory picture compatible with jaundice as usually encountered with phenothiazine derivatives. The relatively few equivocal abnormal hepatic tests were probably not related to drug treatment, as these were sporadic, isolated, or not corroborated by other tests. Clinically important hepatic dysfunction from phenothiazine derivatives is usually associated with recognizable jaundice preceded by fever and prodromal symptoms, and easily corroborated by appropriate laboratory or histologic tests.[6,9] What is important is that abnormal hepatic tests occurring during drug therapy should not always be attributed to subclinical manifestations of drug-induced hepatic dysfunction, as has been done.[4,10]

The interpretation of the changes in temperature, pulse rate, and blood pressure was quite difficult. The infrequency of such changes, despite careful efforts to detect them, was surprising. Some patients had lower than usual body temperatures which varied from occasional to sustained low readings. These low body temperatures may have represented a normal variant for some schizophrenic patients rather than drug-induced hypothermia. Changes in pulse rate were few. None of the recorded blood pressures were below normal physiologic limits, the most frequent change occurring when the initial readings were somewhat higher than usual.

The untoward effects recorded in this controlled study were relatively uncommon and appeared in many instances to be manifestations of spontaneous variations in schizophrenic patients or not due to specific actions of the phenothiazine derivatives. Despite rather careful scrutiny for detecting these abnormalities, their occurrence in the various drug treatment groups was neither frequent nor troublesome. Only 21 of 599 patients were dropped from treatment because of side effects or abnormal laboratory tests, none of which were serious in degree.

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An investigator cannot be too certain of his facts—they are sure to be challenged by someone or other—and further, he cannot take too much pains with his report. He will realise that to tell the exact truth is one of the most difficult things in the world. However much trouble he may take, someone will misunderstand him. But if he describes exactly what he did, and the results obtained, and keeps his inferences well within what his data justify, he can never be wrong. For that reason it is wise to distinguish between inferences and conclusions, because the latter may have to be modified in the light of further evidence.

From "The Spirit of Research—A Plea for Independence"
by Mervyn Gordon, St. Bartholomew's Hospital Journal, June, 1920

Triamcinolone acetonide in the topical treatment of selected dermatoses, with special reference to the effectiveness of the 0.5 per cent concentration

The effectiveness of a 0.1 per cent triamcinolone acetonide cream was evaluated by the method of simultaneous and symmetrical paired comparison with 1 per cent hydrocortisone free alcohol in the same base applied topically by a selected group of patients with dermatoses usually benefited by local corticosteroid therapy. With few exceptions the triamcinolone acetonide 0.1 per cent cream proved to be as effective as the 1 per cent hydrocortisone and sometimes more so. In two other smaller but similarly carefully controlled series of patients, a cream and an ointment containing a higher concentration of triamcinolone acetonide, namely, 0.5 per cent, were compared with 0.1 per cent triamcinolone acetonide in the same cream and ointment bases. The preparations containing the higher concentration of triamcinolone acetonide appeared to be superior in many of the patients. The significance of these findings in relation to their use in practice is discussed.

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Previous observers have reported the general therapeutic superiority of 0.1 per cent triamcinolone acetonide over 1 per cent hydrocortisone as a topical measure in the management of selected dermatoses.[1,2,3,10]

In addition to presenting our confirmatory results with topical triamcinolone acetonide 0.1 per cent as compared with topical hydrocortisone free alcohol 1.0 per cent, the purpose of this paper is to report our new findings on the comparative effectiveness of 0.5 per cent and 0.1 per cent preparations of triamcinolone acetonide. These comparative evaluations were carried out in the treatment of a series of patients suffering from dermatoses ordinarily responsive to the topical use of this group of compounds.

Hydrocortisone was selected as the standard control preparation because of our large clinical and investigative experience with this compound used as a topical agent.[5-9]

The triamcinolone acetonide preparations used in this study were supplied through the courtesy of Dr. Christopher Demos of the Lederle Laboratories Division of American Cyanamid Co., Pearl River, N. Y.

Part I

Method. One-tenth per cent triamcinolone acetonide in an emulsion-type wash-

Table I. *Comparison of 0.1 per cent triamcinolone acetonide cream with 1 per cent hydrocortisone free alcohol cream*

Diagnosis	*No. of cases*	*Triamcinolone acetonide vs. hydrocortisone free alcohol*			
		Triamcinolone more effective	*Both equally effective*	*Triamcinolone less effective*	*Both ineffective*
Atopic dermatitis	29	18	10	1	
Allergic eczematous contact-type dermatitis	8	1	5		2
Hand eczema	2	2			
Psoriasis	2	2			
Seborrheic dermatitis	1	1			
Nummular eczema	1	1			
Pruritus vulvae	1		1		
Familial benign chronic pemphigus	1	1			
Total	45	26	16	1	2

able cream base* was compared with 1 per cent hydrocortisone free alcohol in the identical base.

The method of simultaneous and symmetrical paired comparisons was used for all patients.[4] Each was instructed to rub the triamcinolone acetonide cream into the affected areas of one side of the body and the hydrocortisone free alcohol cream into the symmetrically located affected areas of the other side of the body 3 to 4 times daily. Each patient was seen for follow-up examinations at 1 to 4 week intervals. The criteria for judging improvement included (1) reduction of symptoms (in the main pruritus), (2) lessening of edema, erythema, and/or scaliness, and/or (3) improvement or clearing of the eruption.

Results. The results of the evaluation are noted in Table I. The 0.1 per cent triamcinolone acetonide cream proved to be equal to or more effective than the 1 per cent hydrocortisone free alcohol cream in 42 of 45 patients. In 1 patient it was less effective and in the remaining 2 patients neither drug was effective.

It was also noted that the triamcinolone cream produced complete clearing for the first time in several of the patients who had had the eruptions for many years and had previously used many types of local therapy (including other corticosteroid preparations).

Another favorable effect noted by 5 patients was a more rapid amelioration of symptoms with the use of the triamcinolone acetonide cream than with the hydrocortisone cream, even though both preparations were equally effective in the long run.

Part II

Method. In a smaller series of patients a cream containing a higher concentration of the triamcinolone acetonide, namely, 0.5 per cent, was similarly compared with the 0.1 per cent triamcinolone acetonide in the identical vehicle. In an additional small

*Consisting of spermaceti, stearyl alcohol, Sorbo solution, parabens, Arlacel, Robane, Tween 80 in distilled water.

Table II. *Comparison of 0.5 per cent triamcinolone acetonide cream with 0.1 per cent triamcinolone acetonide cream*

Diagnosis	*No. of cases*	*0.5% better than 0.1%*	*Equally effective*	*0.1% better than 0.5%*
Atopic dermatitis	6	3	3	
Allergic eczematous contact type dermatitis	4	2	2	
Nummular eczema	1			1
Psoriasis	1		1	
Total	12	5	6	1

group of patients a 0.5 per cent triamcinolone acetonide ointment* was compared with a 0.1 per cent triamcinolone acetonide in the identical ointment base.

Results. As recorded in Table II, the 0.5 per cent triamcinolone acetonide cream was more effective than the 0.1 per cent triamcinolone acetonide cream in 5 of the 12 patients treated, and equally effective in 6.

The results with 0.1 and 0.5 per cent triamcinolone acetonide ointments are given in Table III. In this series, the 0.5 per cent triamcinolone acetonide ointment was more effective than the 0.1 per cent triamcinolone acetonide ointment in 7 of the 11 patients, and equally effective in 4.

In the patients who responded best to the triamcinolone acetonide cream or ointment, the response with the 0.5 per cent concentration usually was much more rapid than with the 0.1 per cent concentration or the resultant improvement was of considerably greater degree. In 2 patients, the therapeutic response to the 0.5 per cent preparation was quite dramatic, bringing about complete clearing of the dermatitis, whereas the 0.1 per cent concentration, causing improvement, fell far short of producing complete resolution.

Like the other corticosteroids, triamcinolone acetonide must be used regularly and repeatedly and in chronic dermatoses, often for long periods of time.

There were no instances of allergic sensitivity to the medications nor were there any clinical signs or symptoms to suggest percutaneous absorption. The various preparations were also well accepted by the patients since they do not stain nor do they have any odor. Where lubrication of the affected parts was desirable or necessary, the ointment base was generally preferred to the cream base.

Comments and conclusions

Our experience corroborates that of others who have reported that 0.1 per cent triamcinolone acetonide topical preparations are highly effective anti-inflammatory agents and therapeutically generally somewhat better than similar topical preparations of 1 per cent hydrocortisone. It is currently our feeling that the available triamcinolone acetonide topical preparations are usually the agents of choice for the man-

Table III. *Comparison of 0.5 per cent triamcinolone acetonide ointment with 0.1 per cent triamcinolone acetonide ointment*

Diagnosis	*No. of cases*	*0.5% better than 0.1%*	*Equally effective*	*0.1% better than 0.5%*
Atopic dermatitis	6	4	2	
Psoriasis	2		2	
Stasis dermatitis	1	1		
Allergic eczematous contact-type dermatitis	1	1		
Seborrheic dermatitis	1	1		
Total	11	7	4	

*Consisting of parabens, mineral oil, wool fat, and white petrolatum.

agement of those dermatoses for which topical corticosteroids are indicated.

The 0.5 per cent triamcinolone acetonide cream or ointment was so superior to the 0.1 per cent preparation in a few of the patients that it became quite evident to us that stronger concentrations of this order would be of considerable aid to the practitioner, in particular, the dermatologist, in the management of sometimes stubborn or resistant dermatoses. Creams or ointments of such stronger concentrations of triamcinolone acetonide could be mixed with other creams or ointments containing tars, quinolines, mercurials, antibiotics, agents active against Candida organisms, etc., without greatly reducing the therapeutically effective concentration of the triamcinolone. Of course, it would be better still if triamcinolone acetonide powder, as such, were available so that it could be used by the pharmacist to fill prescriptions. These could then be written by the physician with the indicated concentrations of the steroid, in the proper vehicle and in combination with all and any other effective topical agents.

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Failure of ethylenediamine condensation method to detect increased plasma norepinephrine concentrations during general anesthesia in man

Analysis of human plasma by the ethylenediamine condensation method did not reveal a striking increase in norepinephrine concentration during general anesthesia, although this elevation could be clearly shown both by biologic assay and by the more specific trihydroxyindole method. This discrepancy probably results from the presence in normal plasma of relatively large amounts of biologically inactive catechol substance or substances which interfere with analyses made by ethylenediamine condensation.

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In 1956 one of us[6] expressed doubts that the ethylenediamine (EDA) condensation method[10] was sufficiently specific for estimating catecholamine concentrations in human plasma. Our subsequent experience has confirmed this suspicion. First, measurements made with ethylenediamine condensation failed to agree with those secured by biologic assay. Second, while conditions which enhance sympathetic nervous activity (for example, diethyl ether anesthesia) were associated with increased plasma catecholamine concentrations as estimated either biologically or by the trihydroxyindole (THI) method, the ethylenediamine method failed to detect any consistent change. This reports our recent observations.

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*Wellcome Associate Professor of Research in Anesthesiology.

Methods

Blood was obtained by brachial artery puncture from patients scheduled for elective operations under general anesthesia. It was collected by drawing it into a 30 ml. syringe moistened with heparin (1,000 U.S.P. units per milliliter). When the ethylenediamine method was to be used, a preservative[10] consisting of 2 per cent sodium fluoride and 3 per cent sodium thiosulfate equal in volume to one third of the volume of blood was also added. Samples collected in heparin alone were iced immediately; the others remained at room temperature until centrifuged. Erythrocytes were removed in all cases by centrifugation at 750 g for 20 minutes. Plasma was pipetted off and its pH adjusted at 8.0 to 8.4, either by swirling it in air or (in the case of the ethylenediamine method) by dropwise addition of 0.5 N sodium carbonate.[10] After pH adjustment, every 15

ml. lot of plasma was passed through a 1 Gm. alumina (Woelm) column. The column was washed with glass distilled water (10 ml.) and then eluted with 6 ml. 0.2 N acetic acid.

The eluates were analyzed by three independent methods. In each method known additions (0.004 to 0.04μg) of epinephrine and norepinephrine were made to eluate fractions and the observed response used in the calculations of the unknown concentrations. Eluates to be analyzed by the ethylenediamine method were treated as described by Weil-Malherbe and Bone,[10] with modifications introduced by us.[6] Analysis by the trihydroxyindole method was carried out as described by us.[5] Samples for biologic assay were lyophylized, reconstituted in 0.001 N HCl, and then analyzed using a modification of the rabbit aorta strip technique of Helmer.[2*] Losses (of added epinephrine or norepinephrine) involved in the various steps taken all together did not exceed 30 per cent. When contraction of an aortic strip was produced by an eluate the strip was subsequently treated with an adrenolytic drug (0.5 mg. 1,4-bis[1,4-benzodioxan-2-ylmethyl] piperazine) in order to insure that contraction resulted from the presence of a catecholamine. Results obtained with the biologic method are calculated, assuming the catecholamine present to be norepinephrine. If only epinephrine were present the figures given would be 25 per cent too low, since the aortic strip had slightly greater sensitivity to norepinephrine than to epinephrine.

In every subject, a sample was drawn both before the induction of anesthesia and after maintenance of anesthesia for 30 or more minutes with diethyl ether or cyclopropane. After this, operation was begun. The concentrations of the anesthetics in end-expired air ranged from 15 to 30 volumes per cent cyclopropane and from 2 to 4 per cent diethyl ether, but were relatively constant in each subject. The blood samples drawn before and during anesthesia were analyzed with the same method in each subject and sometimes with more than one method.

Results and discussion

Comparison of methods in normal plasmas. Table I shows the marked disagreement between results obtained by ethylenediamine condensation and by the other two methods in plasma secured before the induction of anesthesia. The difference was in the norepinephrine fraction. Concentrations of norepinephrine estimated by ethylenediamine condensation were five to ten times as high as by either the trihydroxyindole method or biologic assay. Concentrations of epinephrine were the same by both chemical methods.

Comparison of methods in single plasma samples. Despite the fact that recovery of added amounts of epinephrine and norepinephrine was measured and found to be

Table I. *Concentrations of epinephrine and norepinephrine in normal plasma*

Method	*Concentrations (μg/L.) ± S.D.*		*Number of observations*
	Epinephrine	*Norepinephrine*	
Ethylenediamine (EDA)	0.04 ± 0.04	2.02 ± 0.64	9
Trihydroxyindole (THI)	0.04 ± 0.01	0.22 ± 0.15	13
Aortic strip	—	0.25 ± 0.11	6
Significance of differences	None	$p < 0.01$ (EDA vs. others)	

*Modifications of the Helmer method follow: (1) rabbits were killed by injection of air into an ear vein (instead of by concussion and hemorrhage); (2) ethylenediaminetetraacetic acid disodium salt, 0.5 mg., was added to the bath (in order to chelate heavy metals) before addition of catecholamines; (3) the aortic strip was suspended in a clear solution consisting of NaCl (22.5 Gm.), KCl (2.3 Gm.), anhydrous $CaCl_2$ (0.92 Gm.), KH_2PO_4 (0.53 Gm.), anhydrous $MgSO_4$ (0.47 Gm.), $NaHCO_3$ (7.19 Gm.), and dextrose (6.5 Gm.) in 3.25 L. distilled water.

roughly similar by all methods, it is conceivable that there is some difference in recovery when the same substances occur endogenously. In view of this, a comparison of the methods was made in three equal eluate fractions obtained from the same plasma. The blood (120 ml.) was donated by a normal volunteer. It was drawn into syringes moistened with heparin and analyzed as previously described. Preservative was not added. Three 1 Gm. alumina columns were used, and the eluates collected and pooled. The pooled eluate was reduced to dryness, reconstituted as just described, divided into three equal parts, and analyzed by the three methods. The difference between the ethylenediamine and the other methods persisted. The concentrations (uncorrected for losses in recovery) were: by the biologic method, 0.3 μg per liter norepinephrine; by the trihydroxyindole method, <0.1 μg per liter epinephrine and 0.4 μg per liter norepinephrine; by the ethylenediamine method, 0.1 μg per liter epinephrine and 2.0 μg per liter norepinephrine. Another sample was drawn directly into preservative (no heparin) and analyzed in a similar manner. The difference between the three methods was again evident (biologic, 0.4 μg per liter norepinephrine; trihydroxyindole, 0.1 μg per liter epinephrine and 0.3 μg per liter norepinephrine; ethylenediamine, 0.1 μg per liter epinephrine and 5.9 μg per liter norepinephrine).

The difference in results was not attributable to differences in the recovery of epinephrine or norepinephrine from plasma by various methods because it persisted down to the final stage of analysis. The sensitivity of each method was adequate as shown by the response to additions of known quantities of epinephrine and norepinephrine. Moreover, the response to these additions, which were made to plasma eluate fractions, was compared with additions made to reagent eluates in order to establish whether substances present in the plasma inhibited or modified the responses. No effect was found. With these possibilities excluded, the remaining explanation is that the ethylenediamine method detected one or more biologically inactive substances present in plasma which it confused with norepinephrine.

Effect of induction of general anesthesia. Fig. 1 illustrates these results. Comparing concentrations in the same subject before and during anesthesia, a significant increase was detected by both the biologic and trihydroxyindole methods, but no significant change was found with the ethylenediamine condensation method (p values by Student's "t" test are shown over the bars of the graph). These findings indicate that the interfering substance or substances partially disappeared during diethyl ether or cyclopropane anesthesia, and that they were replaced by norepinephrine.

Evidence for the existence and identity of the interfering substances(s). Our evidence for the presence in normal plasma of substances which interfere with estimations by ethylenediamine condensation is based on the failure of results obtained with this method to agree with the other methods employed. Zileli and associates[11] have also compared THI and EDA methods in normal plasma, and obtained significantly higher results with the latter than with the former. They also found that, in the presence of renal disease, the discrepancy, particularly that in norepinephrine concentration, was exaggerated. The interfering substances(s) could be partially removed by dialysis.

There have been reports[9] that plasma concentration of catecholamines are the same by THI and EDA methods, and even the results which Zileli obtained using trihydroxyindole formation are much higher than ours, but both these reports are based on applications of the original THI method of Lund.[4] This method was not suitable in our hands for use in media containing low concentrations of epinephrine or norepinephrine, the results obtained being falsely high. Much of the error results from the omission of certain fluorescing reagents (for example, ascorbic acid), which are

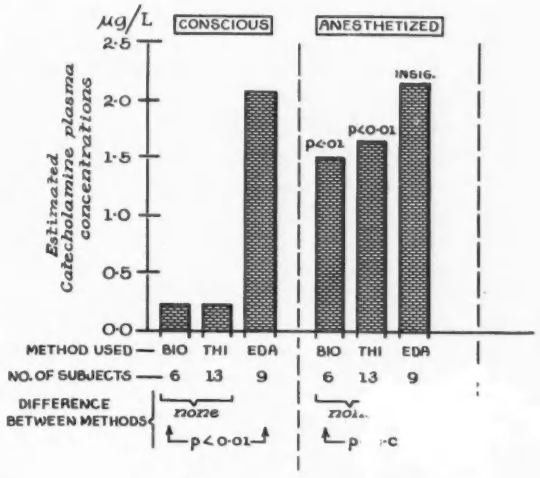

Fig. 1. Ordinate: catecholamine concentrations in micrograms per liter *estimated* by three methods. Probability (p) values *under* the bars indicate significantly higher concentrations estimated by EDA than by other methods. p values *over* the bars on right show that a significant increase in concentration above normal was detected during general anesthesia with either the THI or the biologic method; the EDA method failed to demonstrate this difference.

added to samples, from the blanks. Since these substances contribute to fluorescence measured in plasma eluates, their omission from the blanks causes an overestimation of fluorescence and thus of catecholamine concentration. Authors who have tried to develop trihydroxyindole modifications suitable for analyzing plasma agree with our estimates of catecholamine concentration,[1] and biologic assays by other authors also agree in estimating plasma catecholamine concentrations at less than 1 μg per liter.[3]

In view of this, we return to our conclusion that the ethylenediamine method detects a biologically inactive substance present in plasma and confuses it with norepinephrine. A catechol substance is likely because alumina column chromatography is relatively specific for this configuration. The presence of large amounts (up to 20 μg per liter) of 3:4-dihydroxyphenylacetic acid (dopac) has been reported in bovine plasma[7] and similar quantities were found in two samples of human plasma.* This substance is absorbed by alumina and eluted by weak acid, with recovery estimated at from 60 to 95 per cent.[6,11] It causes fluorescence which is nearly identical in character with that caused by norepinephrine[6,11] with which it would, consequently, be confused by the ethylenediamine condensation technique. Its fluorescence is approximately one sixth as great as that produced by an equal weight of norepinephrine.[6,11] From these data it can be calculated that 15 μg per liter dopac present in plasma would appear to be 2 μg per liter norepinephrine by the ethlyenediamine condensation method. Biologic and trihydroxyindole methods are insensitive to the presence of dopac.[5,8]

The presence of dopac in human plasma thus could explain the divergence between the ethylenediamine and other methods when normal plasma is analyzed. Moreover, it could explain why the ethylenediamine method failed to detect increases in plasma norepinephrine concentration. Dopamine (3:4-dihydroxyphenylethylamine) is believed to be the precursor both of dopac and of norepinephrine,* so that conditions associated with a high norepinephrine synthesis rate (such as increased sympathetic nervous activity) might simultaneously reduce the rate of formation of dopac and thus its plasma concentration.

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The spectacular boom of the drug industry since the beginning of World War II is a phenomenon worthy of close study. It provides a fascinating case history of science involved to the hilt in a world of intense competition, aggressive salesmanship, high profits. The industry offers an enormous variety of products: The list includes valuable medicines that have done much to raise international health standards, anesthetics and tranquilizers for mental patients and germ-killing drugs. There are also preparations of a kind referred to by a distinguished physician of Victorian times: "I firmly believe that if (they) could be sunk to the bottom of the sea, it would be all the better for mankind—and all the worse for the fishes."

FROM "PILL MAKERS AND PEDDLERS" BY JOHN PFEIFFER
THE NEW YORK TIMES BOOK REVIEW, SUNDAY, MARCH 8, 1959.

The stimulant effect of 2-dimethylaminoethanol (deanol) in human volunteer subjects

A double blind comparison of deanol, 10 to 30 mg. base, as the tartrate salt was made with an identical placebo in 35 volunteer subjects. No significant changes from the controls were observed in blood pressures, pulse rate, muscle strength, hand tremor, vital capacity, or body weight. Blood cholesterol levels were not changed. Blood protein bound iodine showed a slight tendency to decrease at the start of therapy, but this was not statistically significant. Gastric acid secretion was not changed, although volume of secretion was. Of the psychological and subjective responses, the significant findings were an increase in muscle tone, better mental concentration, and changes in sleep habits which were (1) less sleep needed, (2) sounder sleep, and (3) absence of the customary period of inefficiency in the morning in the deanol-treated group.

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Deanol,* 2-dimethylaminoethanol, is a metabolic precursor of choline and therefore probably a precursor of cerebral acetylcholine. Reed,[12] working with choline-deficient guinea pigs, finds that deanol will substitute completely for choline, and Demers and Bernard,[3] in similar studies on ducklings, have identical findings. In each of these studies, the workers find aminoethanol, N-methyl-aminoethanol, betaine, dimethylglycine, and methionine to be either inactive or much less active than deanol. Other studies have shown deanol to have a stimulant effect on the central nervous system in animals[6,11] and patients[1,2,8,9,10,14,15] with a variety of disorders. Studies in the mouse with carbon[14]-labeled deanol and choline show that choline is oxidized more extensively than deanol, while deanol attains higher levels in the lipid and acid-soluble fractions of the brain. Label from deanol was retained by the brain, while label from choline was lost continually over the time period studied. An assay of the effects of deanol in normal human subjects therefore was indicated.

Methods

The subjects were 35 second-year medical student volunteers. They were told

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*p-acetamidobenzoate salt marketed as Deaner (Riker Laboratories, Northridge, Calif).

something of the nature of the compound but were not told what effects might be expected. A preliminary physical examination and medical history were obtained on each candidate. One volunteer was not accepted when he was found, before the testing was begun, to have labile hypertension. The group then was a highly homogeneous one of young, healthy adult males, ranging in age from 21 years to 26 years; all were of approximately bright normal intelligence. All were subject to fairly similar schedules and work pressures and followed similar habit patterns. For their participation the students received five dollars plus two dollars for each procedure requiring venipuncture. The project was not connected with any course they were taking.

Deanol was given as the acid tartrate salt in tablet form. An identical-appearing lactose placebo was used. All tablets were dusted with quinine to provide a uniformly bitter taste. They were dispensed randomly in identical glass vials identified only by a code, the key to which was unknown to the dispenser. Each of the test tablets contained the equivalent of 10 mg. of deanol as the base. The instructions to the subjects were to take one tablet each day for the first week, two tablets per day for the second week, and thereafter, they were allowed to take one, two, or three tablets per day ad libitum to allow for individual variation in response. These were taken as a single dose in the morning. The subjects were free to discontinue dosage at any time. None did so.

After 6 weeks of double blind investigation, all of the 35 subjects were given deanol, changing from a controlled experiment to a more freely exploratory investigation. To some who noted no effect from the tartrate during this phase, the lactate was given instead, since it evidently dissociates more freely in the body.* The dose still was 10 to 30 mg. per day.

*Lasslo, A.: Personal communication.

The following observations were made during the 3-month course of the investigations. Once weekly, heart rate, blood pressure, muscle power, hand steadiness, vital capacity, and body weight were measured. Muscle power was measured by the pressure a subject could produce on blowing into a mercury manometer. Hand steadiness was measured by means of a device in which an electrically charged probe was held in a small grounded hole; each contact between probe and hole was counted automatically, and steadiness therefore was inversely proportional to count.

Beginning before the first dose, and once a week thereafter, each subject was asked to complete a questionnaire. This had been made up in part from effects which might be expected from other trials (Fig. 1). Also, to offset giving of cues, some questions were included deliberately to which no positive response was expected. At the bottom of the questionnaire the subject was asked to write in comments.

Before the experiment was begun, a group form of the Rorschach test was given.[13] This was repeated at the conclusion of the series. This test was applied to detect any gross change in quality or quantity of response. For the sake of consistency all inquiry and scoring were done by the same investigator who knew which records came from the initial test and which came from the terminal test; he did not know which subjects had drug and which had placebo. The techniques were mainly those of Klopfer and Kelley.[7]

To explore whether simple capacity for rote learning was affected, memorization of 100 nonsense words was measured before beginning, at the midpoint (6 weeks), and at the conclusion (12 weeks). These words were made up of five letters in the sequence of consonant-vowel-consonant-vowel-consonant, arrived at randomly. Examples are: BUGOG, KUDAT, CEBID, MOVUZ, DINAB. Any accidentally meaningful combination such as KULAK, TETON, REBUS, XEBEC, MONAD was rejected. These were flashed on a screen in groups of 10 for 30

seconds. The subjects were instructed to look at them and to try to memorize as many as possible during that period. They were given 60 seconds to write down as many as they could remember, and then the next group was presented immediately. Only those responses with all five letters correct in proper sequence were rated correct—no partial credit was given. The same set of words was used in each trial. The order of presentation of the 10 groups of 10 words was varied randomly each time.

Twenty of the subjects were submitted to more detailed physiologic measurements. Once weekly, blood counts and urinalyses were done and, at intervals of four weeks, serum protein bound iodine, total cholesterol level, and cephalin-cholesterol flocculation tests were performed in selected subjects.

Eight of the subjects participated in a subexperiment on the effects of deanol on gastric acidity. A plastic Levine tube was introduced into the stomach by way of either the nose or the mouth with the subject in the early morning fasting state. Residual contents were removed and discarded. Then specimens were collected at 15 minute intervals for a total of one hour. This was done once a week for 9 weeks in 6 of the 8 subjects to determine the chronic effect of deanol. Two had to discontinue the procedure because of severe discomfort and some gastric bleeding caused by the intubation. Free acid, total acidity, pH, and volume were measured; titration was done with 0.1 N NaOH, the end point being determined with a Beckman pH meter.

To measure acute effect, the subjects were given 10 to 60 mg. of deanol in 50 ml. of tap water introduced via the Levine

DEANER QUESTIONNAIRE

NAME_____ AGE_____ SEX_____

DOSE THIS WEEK____Tablets.

DIRECTIONS: Circle all of the following which apply to you. Circle more than one in any category where applicable.

OBSERVATIONS TO BE REPORTED WEEKLY

SLEEP	Need more	Need less	Insomnia	Normal
ENERGY (Quant.)	Normal	Increased	Decreased	
" (Qual.)	Purposeful	Restless	Lassitude	
BOWEL HABITS	Diarrhea	Constipation	Normal	Color
URINARY HABITS	Frequency	Oliguria	Conc. Urine	Dilute Urine
THIRST	Normal	Increased	Decreased	
NOSE	Stuffy	Clear	Crusted	URI
EYES	Burning	Normal	Crusted	Tearing
HEADACHES	Frontal	Occipital	Generalized	Decreased
MUSCLE TONE	Masseter	Quadriceps	Neck	Twitching
LIBIDO	Normal	Increased	Decreased	
APPETITE	Normal	Increased	Decreased	
MOOD	Euphoric	Outspoken	Irritable	Calm
CONCENTRATION	Normal	Increased	Decreased	
HANDS	Warm	Cold	No change	Sweating
MOUTH	Dry	Increased salivation	Normal	

REMARKS: (Please clarify any of the above symptoms.)

OBSERVATIONS: B.P.: Pulse: Weight: Steadiness: Power:

Fig. 1.

Table I

	Measurement at end of first week (10 mg./day)	*Measurement at end of second week (20 mg./day)*
Physiologic measurements		
Systolic blood pressure (mm. Hg)		
Placebo group	124.7	127.1
Deanol group	124.6	124.6
Diastolic blood pressure (mm. Hg)		
Placebo group	81.5	80.2
Deanol group	80.4	80.5
Heart rate		
Placebo group	81.6	79.1*
Deanol group	78.2	75.2*
Muscle power (mm. Hg)		
Placebo group	98.9†	112.0†
Deanol group	106.0	105.0
Vital capacity (L.)		
Placebo group	4.7	4.6
Deanol group	4.6	4.5
Body weight (pounds)		
Placebo group	174.3‡	174.2
Deanol group	164.4‡	164.8

	Smallest hole with 10 contacts or less in 30 seconds			
	4 mm. diameter	*5 mm. diameter*	*7 mm. diameter*	*Total*
Hand steadiness				
Placebo group at end of first week	5	9	2	16
Placebo group at end of second week	6	8	2	16
	11	17	4	32
		$\chi^2 = 0.5$ df = 2	p > 0.9	
Deanol group at end of first week	2	10	1	13
Deanol group at end of second week	6	7	2	15
	8	17	3	28
		$\chi^2 = 1.3$ df = 2	p > 0.5	
Placebo group at end of first week + 2	11	17	4	32
Deanol group at end of first week + 2	8	17	3	28
	19	34	7	60
		$\chi^2 = 0$		

*t = 1.03; p > 0.05.
†t = 1.56; p > 0.05.
‡t = 24.3; p ≪ 0.01.

tube, after a one-half hour basal collection. Another half hour was allowed for absorption, and then aspiration was resumed for 45 minutes. The specimens were assayed as just described.

Results

Except in certain instances which are noted, the results and statistical analyses reported here are taken entirely from the first 2 weeks, while the investigation was

double blind, and all tests subjects were still receiving the same doses, i.e., 10 mg. per day for the first week and 20 mg. per day for the second.

In serial determinations of blood pressures, there were no significant differences between the two groups in mean levels of systolic and diastolic blood pressures, nor were there significant changes in either group's mean from week to week. Similarly there were no changes in heart rate, muscle power, hand steadiness, vital capacity, or body weight. These results are summarized in Table I. It is to be noted that our two groups were not well matched in body weight; the group receiving placebo turned out to be significantly heavier.

There were no significant changes in cephalin-cholesterol flocculation, serum cholesterol, or protein bound iodine (Table II). The downward drift of protein bound iodine after beginning dosage with deanol was not significant.

In the study of gastric acidity, there was no change, either acutely or chronically in total acid produced, although there was a long-term decrease in the volume of secretions (Table III). These laboratory determinations extended past the period of the first 2 weeks.

The questionnaire was aimed at sampling subjective effects. Again these results are taken from the period of the first 2 weeks. As will be evident from the directions given on the questionnaire (See Fig. 1), each subject was free to give more than one response to each item. In the data presented, there are at least two for each, one taken at the end of the first week of

Table II. *Effect of deanol 10 to 30 mg. per day on blood cholesterol (Chol.) and protein bound iodine (PBI)—18 subjects, average age 21 years*

(Means ± Standard Deviations)

	Placebo	*Placebo*	*Deanol*
12 subjects	3-11-57	4-8-57	5-9-57
Ave. Chol.	202.3 ± 44	212.0 ± 49	213.3 ± 45
Ave. BPI	6.5 ± 1.0	6.2 ± 1.6	6.0 ± 1.0
	Placebo	*Deanol*	*Deanol*
6 subjects	3-11-57	4-8-57	5-9-57
Ave. Chol.	216.4 ± 31	210.7 ± 32	212.6 ± 36
Ave. PBI	6.2 ± 1.6	5.4 ± 0.9	5.8 ± 1.6

Table III. *Gastric analysis (N=6)*

	Week								
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
Chronic dosage									
A. Mean volume* produced after aspiration of basal contents	116.0	93.3	73.0	54.2	51.7	61.7	43.7	42.5	54.2
B. Mean volume† acid produced after aspiration of basal contents (mEq.)	3.79	1.91	2.86	1.77	1.84	2.84	1.86	1.50	2.75
Acute dosage									
A. Mean volume									
Before dosage					35.8‡				
After dosage					44.8‡				
B. Mean acid (mEq.)									
Before dosage					1.82§				
After dosage					1.27§				

*F = 3.62; df = 8 and 45; p < 0.05.
†F = 0.677; df = 8 and 45; p = ≫0.05.
‡t = 0.24.
§t = 0.55.

Table IV. *Questionnaire results*

	χ^2	*df*	*p*
Sleep	4.33	1	< 0.05
Energy (quant.)	3.0	3	> 0.5
Energy (qual.)	2.6	4	> 0.5
Bowel habits	3.1	2	> 0.05
Urinary habits	*		
Thirst	*		
Nose	0.98	1	> 0.3
Eyes	*		
Headaches	*		
Muscle tone	6.5	2	< 0.05
Libido	*		
Appetite	*		
Mood	*		
Concentration	8.7	2	< 0.02
Hands	2.6	2	> 0.2
Mouth	*		

*Not calculated, no difference by inspection.

dosage, the second at the end of the second week. The results are summarized in Table IV.

Mental concentration was rated "improved" by 7 of the 17 subjects on deanol. These occurred predominantly at the end of the second week, when the dosage had been 20 mg. per day. This gave a p of less than 0.02 when tested by the chi-square technique. There were also nonspecific changes in muscle tone ($p < 0.05$) and sleep habits ($P < 0.05$). From the comments recorded at the bottom of the questionnaire, the changes in sleep habits were generally: (1) less sleep needed, (2) sounder sleep, and (3) reduced inefficiency in the early morning. These comments were not evaluated statistically. The matrices for items with significant results are shown in Tables V, VI, and VII.

At the end of both series of trials an individual interview was held with each of the subjects. Twenty-five reported some variety of favorable effect, such as "improved mood," "relief of headaches," "clearer thinking," etc. Of the remainder, 5 did not try the lactate salt, having observed no effect from the acid tartrate; the rest noted no effect from either salt. None reported any adverse effects. An interesting and unexpected observation which emerged was that some of those who reported no effect were noted by their friends to have become more agreeable or socially outgoing.

The learning curve for the nonsense words showed a typical steep rise from the

Table V. *Effect of deanol on mental concentration (item on questionnaire)*

	Placebo group N = 18*	*Deanol group* N = 17*	*Total*
Normal	33	29	62
Increased	2	8	10
Decreased	5	0	5
Total	40	37	77

$\chi^2 = 8.72$ df = 2 $p < 0.02$

Table VI. *Effect of deanol on muscle tone (item on questionnaire)*

	Placebo group N = 18	*Deanol group N = 17*	*Total*
All symptoms* pooled	2	10	12
No change†	24	20	44
No response‡	12	8	20
Total	38	38	76

$\chi^2 = 6.49$ df = 2 $p < 0.05$

*Includes all symptoms of increased tone, twitching, aching, etc.

†"No change" means the subject reported that he observed no change.

‡"No response" means he gave no observation.

Table VII. *Effect of deanol on sleep (item on questionnaire)*

	Placebo group N = 18	*Deanol group N = 17*	*Total*
All changes pooled*	24	19	43
"Normal"	33	57	90
Total	57	76	133

$\chi^2 = 4.33$ df = 1 $p < 0.05$
Yates correction not applied since f > 10 in all cells.

*Includes "Less sleep needed," and "Insomnia."

Table VIII. *Learning of nonsense words*

Group	Trial 1	Trial 2	Trial 3
a. Mean number right ± standard deviation			
Control (N = 18)	10.3* ± 4.3	16.3 ± 4.1	17.9 ± 5.3
Deanol (N = 17)	13.4* ± 4.7	19.0 ± 5.6	21.7 ± 4.6
b. Mean number attempted			
Control (N = 18)	27.7 ± 6.1	26.7 ± 4.9	26.3 ± 5.6
Deanol (N = 17)	29.8 ± 5.9	30.4 ± 3.9	31.0 ± 4.3
c. Mean ratio of number right to number attempted			
Control (N = 18)	0.38† ± 0.15	0.63 ± 0.18	0.62 ± 0.17
Deanol (N = 17)	0.46† ± 0.16	0.62 ± 0.17	0.70 ± 0.15

*$\chi^2 = 1.204$; $p > 0.05$.
†$t = 1.47$; $p > 0.05$.

Table IX. *Summary of results of Rorschach test on medical student volunteers before and after chronic dosage with 2-dimethylaminoethanol*

The following Rorschach variables were examined by means of chi-square with the results noted:

R	$0.1 < p < 0.2$
R alternative method	$0.3 < p < 0.5$
W	$0.5 < p < 0.7$
D	$0.5 < p < 0.7$
Dd	$0.5 < p < 0.7$
M	*
FM	*
F	$p = 0.3$
F+	$0.9 < p < 0.95$
K	*
C	$0.8 < p < 0.9$
H	*
A	$0.5 < p < 0.7$
P	*
VIII-X	*

The following were examined by means of t test with the results noted:

F/R	$t = 0.163$	$0.5 < p < 0.9$
F+/F	$t = 1.57$	$0.1 < p < 0.5$

*Not formally calculated; no difference by inspection.

first to the second administration, with leveling off thereafter. In none of the trials was there any significant difference between the groups in total number right, increment in number right, or ratio of number right to number attempted (Table VIII).

The Rorschach test showed no consistent changes in the records of individuals, nor were there significant differences between the groups on either administration, on the basis of either an over-all interpretation or of 17 variables of the psychogram (Table IX).

Discussion

From these results it is evident that deanol at the dosage used produces no notable physiologic change in normal human beings and that at this dosage it has no effect upon gross personality structure or upon rote learning. It does appear to have subjective effects of improving concentration, increasing muscle tone, and changing sleep habits. At the low dosage used in this investigation the effect is sometimes subtle and may be more obvious to others than to the one taking the compound. This dose is known now to be rather small, and the acid tartrate is a relatively unsatisfactory salt because of its poor dissociation and absorption.[5]

Summary

In double blind study in normal young adult human males, doses of 10 to 30 mg. of deanol produced statistically significant subjective changes in mental concentration and muscle tone. It also produced nonspecific but significant alteration of sleep

habits, such as sounder sleep, less sleep needed, and clear-minded awakening. No untoward effects were encountered, and laboratory tests did not disclose any gross changes from normal.

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Laxative studies

I. Human threshold doses of white and yellow phenolphthalein

Studies of threshold laxative response were conducted on 15 males and 10 females between 20 and 45 years of age, by a double blind method over a period of a year. The threshold laxative dose of white phenolphthalein averaged 68 mg. for the males and 36 mg. for the females; for yellow phenolphthalein, 47 mg. and 32 mg., respectively. This study suggests that the factor of sex should be considered in establishing a threshold dose for this product.

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Phenolphthalein is made by condensing phenol with phthalic anhydride under prescribed conditions. A dark reaction product is obtained which, on treatment with decolorizing agents, yields yellow phenolphthalein. Further purification removes more and more color until finally white phenolphthalein remains. Both yellow and white phenolphthalein are safe and effective laxatives. In spite of chemical efforts for many years, the identity of the impurity giving the yellow color has not been determined, although it has been found to be a laxative. U.S.P. XV recognizes white phenolphthalein with the suggested usual dose of 60 mg. Many commercial laxatives contain white phenolphthalein, yellow phenolphthalein, or a mixture of the two. Attempts to develop the bioassays for various cathartics [illegible] laxatives have revealed marked differences in susceptibility of different animals, as well as of different species, to these products.[1] This study was planned to develop a bioassay for the phenolphthaleins, and to assist in further research studies for identification of the yellow impurity (or impurities). A reference standard of white and yellow phenolphthalein were made available for use in this investigation.

As our results developed, it appeared that the factor of sex was playing an important role in determining threshold dosage. Larger doses were being required by males than by females of the same general age bracket. Search of the literature, and conferences with our clinical associates, failed to reveal information regarding any other drug for which the same type of response differed significantly as related to the factor of sex as was noted in these studies.

This study was conducted on 25 healthy adults, 15 males and 10 females, between

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20 and 45 years of age. During the period of a year, some five hundred doses were administered. No other laxative was taken nor were there any significant changes in diet. Weighed quantities of each phenolphthalein were triturated with weighed amounts of lactose, then a definite quantity of the mixture was packed in each of a series of capsules. The capsules were similar in appearance and contained from 0 to 100 mg. of white or of yellow phenolphthalein. Each set of capsules was given a code letter, which was revealed neither to the investigators nor to the subjects during the course of the double blind investigation. At weekly intervals, each collaborator was handed a coded envelope which contained two capsules to be taken at bedtime.

The frequency and the consistency of stools passed for several weeks before the start of this study, and daily throughout the course of the investigation, were recorded. A null response ("O") was recorded when no change was observed within two days after taking any lot of capsules. A threshold response ("1") was an increase in the total number of stools, in the passage of one or two soft or unformed stools instead of stools of normal consistency, or in both changes. A response of "2" was an increase in the number of stools, which were unformed or very loose, during a period of several days, either griping or cramps, or both developments. A reaction of "3" was interpreted as marked cramps or griping, accompanied by a marked increase

Table I. *Order of laxative response to white phenolphthalein*

Subject No.	*Total dose (mg.)*											
	0	6.25	12.5	25	37.5	50	62.5	75	100	125	150	200
Males												
1	00	—	000	11*	1	12	—	1	—	—	—	—
2	001	—	—	0	1*	3	—	—	—	—	—	—
3	000	—	—	00	11*	111	—	1	1	—	—	—
4	00	—	—	01	10	11*	—	1	1	—	2	—
5	00	—	—	—	100	1111*	—	1	111	2	—	—
6	00	—	—	0	00	111*	—	1	3	—	—	—
7	0	—	00	00	—	11*	—	011	11	1	—	—
8	000	—	—	0	01	311*	—	2	—	—	—	—
9	0	—	—	—	—	011*	1	11	1	11	—	—
10	00	—	—	00	—	011*	2	22	—	—	—	—
11	012	—	—	—	—	2*	—	2	12	—	—	—
12	00	—	—	—	—	00	1	0112*	22	—	—	—
13	00	—	—	—	—	1	—	010	211*	—	—	—
14	00	—	—	—	—	0	—	0	01	—	11*	2
15	00	—	—	—	—	0	—	0	00	—	01	31*
Females												
1	00	1	101*	201	1	3	—	—	—	—	—	—
2	00	000	12*	1	—	3	—	—	—	—	—	—
3	000	—	00	11*	2	0111	—	3	—	—	—	—
4	000	—	—	012*	11	211	—	—	—	—	—	—
5	000	—	—	00	11*	122	—	—	—	—	—	—
6	000	—	—	0	11*	1	—	1	1	2	—	—
7	00	—	—	0	00	111*	—	1	—	—	—	—
8	00	—	—	00	—	101*	—	12	—	—	—	—
9	00	—	—	—	00	110*	—	22	—	—	—	—
10	000	—	—	—	—	010	21*	122	—	—	—	—

*Indicates the threshold dose, selected on a basis of the responses of the subject to the entire series of doses of each product.

Table II. *Order of laxative response to yellow phenolphthalein*

Subject No.	*Total dose (mg.)*											
	0	6.25	12.5	25	37.5	50	62.5	75	100	125	150	200
Males												
1	00	—	—	0	21*	33	—	—	—	—	—	—
2	001	—	—	1*	—	—	—	—	—	—	—	—
3	000	—	100	12*	—	11	—	2	—	—	—	—
4	00	—	—	0	—	00	—	11*	1	2	—	—
5	00	—	—	0	01	2122*	—	2	—	—	—	—
6	00	—	—	0	0	101*	12	3	—	—	—	—
7	0	—	—	0	00	111*	—	12	1	—	—	—
8	000	—	—	0	011*	312	—	—	—	—	—	—
9	0	—	—	000	21*	2	—	—	—	—	—	—
10	00	—	00	211*	—	111	—	2	—	—	—	—
11	012	—	—	3*	—	2	—	2	—	—	—	—
12	00	—	—	00	11*	2	—	2	—	—	—	—
13	00	—	—	00	—	111*	—	1	1	—	—	—
14	00	—	—	0	—	00	—	11*	11	2	—	—
15	00	—	—	0	—	101	—	100	21*	—	—	—
Females												
1	00	—	00	1101*	12	—	—	—	—	—	—	—
2	00	00	11*	1	—	3	—	—	—	—	—	—
3	000	—	—	00	01*	22	—	—	—	—	—	—
4	000	—	1	1*	—	012	2	2	—	—	—	—
5	000	—	—	101*	2	2	—	—	—	—	—	—
6	000	—	100	1111*	—	2	—	—	—	—	—	—
7	00	—	—	110	—	001*	2	2	—	—	—	—
8	00	—	—	0	101*	012	2	2	—	—	—	—
9	00	—	0	0111*	2	3	—	—	—	—	—	—
10	000	—	—	11	—	00	11*	2	—	—	—	—

*Indicates the threshold dose, selected on a basis of the response of the subject to the entire series of doses of each product.

in the number of passages, and followed by no stools for one or more days. Side effects such as skin reactions were sought, but none developed during the course of the entire investigation.

Successive doses of placebo or either white or yellow phenolphthalein were administered at random dosage levels until the quantity was determined which produced a threshold response "1." A placebo was given at irregular intervals throughout the study to prevent the possible development of conditioned reflexes to capsules. The degrees of laxative response to successive doses of white phenolphthalein are recorded in Table I, and to yellow phenolphthalein in Table II. The values are reported in the order in which the indicated dose was administered. There appears to

Table III. *Threshold doses of phenolphthaleins to males*

Subject No.	*White (mg.)*	*Yellow (mg.)*	*Relative potency (white = 100%)*
1	25	37.5	67
2	37.5	25	150
3	37.5	25	150
4	50	75	67
5	50	50	100
6	50	50	100
7	50	50	100
8	50	37.5	133
9	50	37.5	133
10	50	25	200
11	50	25	200
12	75	37.5	200
13	100	50	200
14	150	75	200
15	200	100	200
Mean ± S. E.	68 ± 12	47 ± 4	147

be a trend toward increasing response to certain doses on repetition, which suggests some increase in sensitivity but not any tolerance. In an analysis of the results, after administration of alternate doses of yellow and of white phenolphthalein, no changes in degree of response were found to indicate any residual effects.

Considering the responses of each subject to the entire series of doses of each product, the threshold dose was selected, which is indicated by an asterisk in the tables. These chosen doses for both phenolphthaleins in males are consolidated in Table III, and for females in Table IV. The potency of yellow phenolphthalein ranged from 67 to 200 per cent, averaging 147 per cent for the males and 115 per cent for the females in this study.

For the 15 males, the threshold dose of white phenolphthalein ranged from 25 to 200 mg., and averaged 68 mg. The standard error was found to be 12.3 mg. This dose is in substantial agreement with the 60 mg. usual dose suggested in the U.S.P., and 11 of the 15 subjects showed threshold values below this dose. Similarly, the threshold dose of yellow phenolphthalein for these same subjects ranged from 25 to 100 mg., averaging 47 mg. with a standard error of 4.3 mg. (Fig. 1). Curiously, 2 males were more susceptible to white than to yellow phenolphthalein and at different threshold

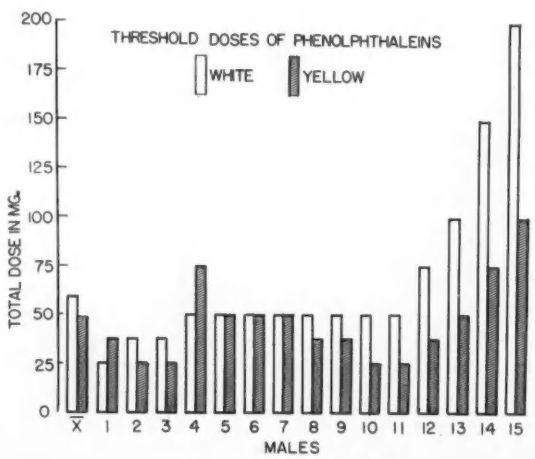

Fig. 1.

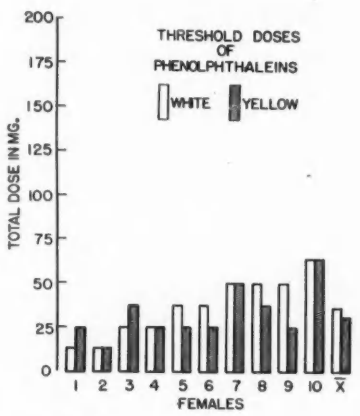

Fig. 2.

dosage levels, although the others were more susceptible to yellow phenolphthalein (Table III).

For the 10 females, the threshold doses of white phenolphthalein ranged from 12.5 to 62.5 mg., averaging 36 mg., with a standard error of 5.4 mg. (Table IV). The threshold doses of yellow phenolphthalein ranged from 12.5 to 62.5 mg., averaging 32 mg., with a standard error of 4.5 mg. (Fig. 2). Two of the 10 women were more susceptible to white than to yellow phenolphthalein, although in the other 8 cases the usual response of greater potency of the yellow product was shown.

The differences in threshold values for the white and the yellow phenolphthaleins for the male and the female subjects in this study are consolidated in Table V. The average threshold doses for both products are seen to be greater for the male than for the female subjects. These differences are roughly proportional to the average body weights. The threshold dose of white phenolphthalein for the male subjects was 68 mg. or approximately 1 mg. per kilogram. Combining results for both sexes, the average threshold dose for white phenolphthalein was found to be 56 mg. The yellow product was about one third more potent.

A few studies were made on combinations of white and yellow phenolphthalein, giving known proportions of their respective thresholds. The results indicated that the laxative potencies were additive, that

Table IV. *Threshold doses of phenolphthaleins to females*

Subject No.	*White (mg.)*	*Yellow (mg.)*	*Relative potency (white = 100%)*
1	12.5	25	50
2	12.5	12.5	100
3	25	37.5	67
4	25	25	100
5	37.5	25	150
6	37.5	25	150
7	50	50	100
8	50	37.5	133
9	50	25	200
10	62.5	62.5	100
Mean ± S. E.	36 ± 5.4	32 ± 4.5	115

Table V. *Sex differences in phenolphthalein thresholds*

Sex	*No.*	*Threshold Doses (mg.)*		*Relative potency of yellow*
		White	*Yellow*	
Male	15	68 ± 12.3	47 ± 4.3	147
Female	10	36 ± 5.4	32 ± 4.5	115
Both	25	56	43	137

is, one half of the threshold dose of each product produced the expected threshold response, when administered in combination.

Conclusions

1. Administered once weekly in gelatin capsules, the threshold laxative dose of white phenolphthalein averaged 68 ± 12 mg. for 15 males, and 36 ± 5 mg. for 10 females.

2. The threshold dose of yellow phenolphthalein for the same subjects was 47 ± 4 mg. and 32 ± 4 mg., respectively.

3. The U. S. P. suggested usual dose of 60 mg. of white phenolphthalein had a laxative effect upon three fourths of the males, and all of the females in this study. The same dose of this yellow phenolphthalein produced a positive response in all but 3 of these collaborators.

4. This study suggests that the factor of sex may need to be considered in establishing the dose of a laxative.

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Role of antihistamine therapy in diphenylhydantoin-induced gingival hyperplasia

A clinical and histopathologic evaluation

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Stimulated by the original report of Gaillard upon the favorable influence of chlorprophenpyridamine maleate† on diphenylhydantoin‡-induced gum hyperplasia, and the reports of Breg and Sturmer indicating that chlorprophenpyridamine maleate and other antihistamine drugs were of no effect on diphenylhydantoin-induced gum hyperplasia, the authors have studied 35 patients with this condition to a marked degree.

In spite of the work of the previous investigators, our evaluation was felt warranted because of our use of a carefully controlled double-blind experimental technique.

Our patients were given either chlorprophenpyridamine maleate or an identical-appearing placebo. Placebo or antihistamine drugs were administered for a 17 week period, and clinical grading, photographic grading, and gum biopsies were performed upon each patient before and after the administration of the drugs.

In a well-controlled experiment we demonstrated that chlorprophenpyridamine maleate† produced no evident visual or histopathologic change in diphenylhydantoin-induced gum hyperplasia.

Recently there have been several reports regarding the use of antihistamine therapy in the treatment of diphenylhydantion‡ gingival hyperplasia.

Gaillard[1] originally reported in January, 1957, that chlorprophenpyridamine maleate* was effective in relieving diphenylhydantoin-induced gum hyperplasia in 2 cases.

Breg and Falcetti[2] reported a series of 7 cases in which no improvement occurred after treatment with chlorprophenpyridamine maleate in doses of 8 to 12 mg. twice a day for a period of 10 weeks.

Sturmer[3] reported on a series of 28 patients to whom antihistamines were given

These studies were carried out at the State Colony and Training School, Pineville, La.

*Staff physician at the State Colony and Training School, Pineville, La.

†Teldrin.

‡Dilantin.

*Teldrin.

for treatment of gingival hyperplasia secondary to the administration of diphenylhydantoin sodium. His patients ranged from 4 to 32 years of age and were given chlorprophenpyridamine maleate, 4 mg. every 6 hours; tripelennamine hydrochloride* was given to 5 patients in doses of 50 mg. every 6 hours; and diphenhydramine hydrochloride† to 5 patients, 25 mg. every 6 hours. Colored photographs were made of the gingivae before institution of therapy and upon the completion of therapy. This author found no change in the degree of hyperplasia following treatment with antihistamines.

We felt that a careful double-blind investigation utilizing placebo and drug was warranted; we also utilized gingival biopsy before and after administration of the medication.

Method

Patients at a state institution for the mentally retarded were used as subjects for this experiment. All patients except 2 were receiving diphenylhydantoin in doses of 200 to 400 mg. daily. Two patients were receiving phenylethylhexahydropyrimidine dione‡ alone, and 5 patients received this drug in addition to diphenylhydantoin.

Eleven males and 6 females of various ages were placed in one group and 10 males and 8 females of comparable ages were placed in the second group (Table I).

Group B received chlorprophenpyridamine maleate§ sustained release capsules of 12 mg. twice daily and Group A received an identical-appearing placebo. The drug and placebo were coded and the results kept secret from all investigators until completion of the experiment and tabulation of the results. The drug and placebo were given for an uninterrupted period of 17 weeks.

*Pyribenzamine.

†Benadryl.

‡Mysoline.

§Teldrin spansules, placebo, and photographic materials were supplied by Smith Kline & French Laboratories.

Before administration of drug the patients were graded clinically on a 0 to 4 scale according to the extent of hyperplasia evident, as shown below:

0 No hyperplasia
1+ More than half of tooth exposed, no interdental hyperplasia
2+ More than half of tooth exposed, with interdental hyperplasia evident
3+ Less than half of tooth exposed, with interdental hyperplasia
4+ Marked coverage of tooth with pronounced interdental hyperplasia

The patients were again clinically graded at the end of the experimental period.

Colored photographs of the gums were obtained in 21 cases before and after drug administration, and these films were independently rated by each investigator by the above grading scale.

Gingival biopsy specimens were obtained in all cases before and after the period of antihistamine treatment. Because of the small size of the biopsy specimen it was necessary to grade only marked differences, with three categories, minimal (1 plus), moderate (2 plus), and severe (3 plus). Two processes were graded separately. These were the degree of epithelial hyperplasia and the degree of marginal periodontal inflammation.

Results

Data for the two groups, A (placebo) and B (chlorprophenpyridamine maleate), were analyzed and are compared in Table II.

Table. I. *Age and sex distribution of drug and placebo groups.*

	Age (decade)		
	2nd	*3rd and 4th*	*4th and over*
	Group B (Drug)		
Male	4	4	2
Female	2	5	1
	Group A (Placebo)		
Male	8	2	1
Female	1	4	1

Table II. *Changes in degree of gum hyperplasia in drug and placebo groups*

Change in grade of hyperplasia	*Clinically and photographically*	*Clinically only*	*Total*
	Drug		
1 degree less	4	0	4
No change	1	6	7
1 degree more	5	0	5
Total	10	6	16
	Placebo		
1 degree less	5	1	6
No change	2	7	9
1 degree more	2	0	2
Total	9	8	17

The clinical results show that in neither group, A or B, were there changes which could not be expected from chance alone or from the observer-difference in grading by categories.

Microscopic study of gingival biopsy specimens in all pretreatment groups revealed epithelial hyperplasia to be marked in all but 9 cases, which were of moderate severity. No case showed epithelial hyperplasia minimal in severity.

The marginal periodontitis varied more, but most specimens were of moderate-to-marked severity. Only 2 cases showed minimal periodontitis. Comparison of the post-treatment group, both control and treated cases, showed similar findings, with no histopathologic evidence of a diminished degree of epithelial hyperplasia or marginal periodontitis.

Conclusions

Our results fail to demonstrate any visually or histopathologically significant effect of administration of chlorprophenpyridamine maleate upon the gingival hyperplasia induced by diphenylhydantoin administration.

The authors are indebted to Dr. Ralph Lampert, Medical Director at the State Colony and Training School, Pineville, Louisiana, for his assistance in making this study possible.

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The pharmacologic basis of the treatment of myasthenia gravis

The origins of the modern treatment of myasthenia gravis go back to the fundamental work of Loewi and Dale, identifying a chemical transmission at the myoneural junction related to the enzyme cycles built around acetylcholine. The normal cycle is described involving cholinesterase and choline acetylase to restore the enzyme to its normal state. Abnormal cycles including competitive block due to curare-like substances as well as equally serious depolarizing block from too much anticholinesterase compound present, and similarities and differences between curare poisoning and myasthenia are discussed. The difficulties in controlling the symptoms of myasthenia are described in detail. It is shown that many patients can be restored to only 50 or 60 per cent of normal and that the most effectual and carefully selected medication achieves 80 to 95 per cent normality in only about one fourth of the patients; in another fourth well over 50 per cent normalcy is reached. There is, however, a third group who attain only 40 to 60 per cent normalcy, and a final group of patients who cannot reach even 40 per cent of normal function on the most effective currently available medication.

The differential findings and diagnosis of myasthenic crisis and cholinergic crisis are discussed in detail. The difficulty and complexity of treating this disease are stressed.

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The clinical syndrome known as myasthenia gravis was first described in 1671 by Willis.[1] The classic descriptions by Erb[2] and Goldflam[3] in the latter part of the nineteenth century emphasized the lack of any gross or microscopic findings at postmortem examinations of brain, muscles, and nerves. As a result there was no specific part of the body that suggested therapeutic attack. Indeed, until 1930, treatment with various drugs, physiotherapy, and special diets was without any objective evidence of improvement or even temporary alleviation of symptoms.

In 1930 Dr. Harriet Edgeworth,[4] who had myasthenia, by chance found that ephedrine sulfate taken for a sinus infection relieved her symptoms partially. Empirically then, without pharmacologic basis, this drug was used for some years with some success in alleviating the symptoms encountered.

In 1934 Dr. Mary Walker[5] tried physostigmine injections to overcome the dys-

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phagia, diplopia, and ptosis that her patients showed. Her remarkable success not only began the era of practical therapy of the disease, but clarified, to a certain extent, the nature of the disturbance. Dr. Walker had been told that the condition resembled curare poisoning, the antidote of which was physostigmine. Her successful application of this drug and later its synthetic analogue, neostigmine, as therapy had both an empiric and a pharmacologic rational basis. It was known from the experiments of Claude Bernard[6] that curare produced a chemical disturbance at the myoneural junction, blocking a normal nerve impulse from reaching a normally responsive muscle fiber. J. Pal[7] had found that physostigmine corrected this in some way and identified this alkaloid as an antidote for curare poisoning in 1900. The disease now had a site at the myoneural junction even if it had no gross or even microscopic pathologic lesions in this area.

It might be well at this point to define and describe the symptoms of this disease of the myoneural junction. The outstanding and constant finding is a pathologic and rapid exhaustion of voluntary muscular contractions. After the initial contraction occurs, the second, third, and fourth ones are reduced in amplitude steadily until they are no longer possible. If the contractions are measured by means of an ergograph, this steady decrement in amplitude constitutes the characteristic fatigue curve of this disorder. While it is true that the normal muscle, if it is given a *heavy* task of work to perform, shows a similar-appearing fatigue curve, the difference between normal fatigue and that of the myasthenia patient is very great. The loss of amplitude as the voluntary act is continued reaches the zero point *10 times as fast* in the patient with myasthenia as in the normal subject.

Sixty-five years ago Jolly[8] demonstrated this rapid exhaustion of the muscle by using a faradic stimulating current and rapidly stimulating the muscle to contract at a rate of 90 times in a minute until no further response was visible. In myasthenia this occurred in a fraction of a minute where at this rate it could go on indefinitely in the normal person. The Jolly reaction, as it is called, is essentially the basis for the more complicated and advanced electrical stimulation and recording that are used today. These will be described later in this article.

After a pathologically long period of rest, however, the myasthenic muscle can again contract, and the fatigue curve is repeated. The second characteristic of myasthenia gravis is a pathologically slow return to the previous state after a certain period of rest. Again, we must look at the normal recovery of a muscle after heavy work on a voluntary basis, and see that, in myasthenia gravis, not only is there rapid exhaustion or fatigue of the muscle under either voluntary or electrical stimulation, but an unusual or pathologically long period of time is also required for the muscle to recover its original ability to contract. A voluntarily driven bulb ergograph, which has been in use in our laboratory since 1951, has been so constructed that the squeeze of the bulb at an interval of 1 second produces only slight fatigue in the normal person after 2 minutes. Thus, it is possible for him to squeeze the bulb 120 times with little drop in amplitude (Fig. 1). In order to produce a similar curve of *no fatigue* with the bulb ergograph in a patient moderately afflicted with myasthenia gravis, it is necessary to provide an interval of rest between each voluntary contraction of 6 to 20 seconds (Fig. 1).

The disorder is essentially in the recovery phase of the muscle action cycle. The rapid fatigue is simply due to inadequate time for this recovery to take place before the next impulse is received. For example, the levator oculi muscles holding the eyes open in the normal subject have every 3 or 4 seconds a brief rest resulting from the spontaneous blink. A 0.5 second rest is all that is needed for complete recovery of the normal muscle. In myasthenia gravis, where 3 to 10 seconds' rest may be needed,

the muscle is rapidly exhausted, resulting in the ptosis so common in this disease.

Normal activity such as standing, keeping the head erect, walking, all involve alternate periods of muscular activity with brief but adequate periods of rest or inactivity. Where this normal ratio of activity to rest (8 to 1) becomes altered, as in holding the head in a rigid, fixed posture where there is no rest, the normal muscle soon develops marked signs of fatigue. In Parkinson's disease, too, these necessary periods of muscular rest are lost so that fatigue, weakness, and reduced muscular performance are conspicuous symptoms.[9]

One might well define myasthenia gravis as fatigability of those muscles which are not fatigued in normal activity, as the muscles used in moving the eyes, swallowing, talking, and in breathing. This diffi-

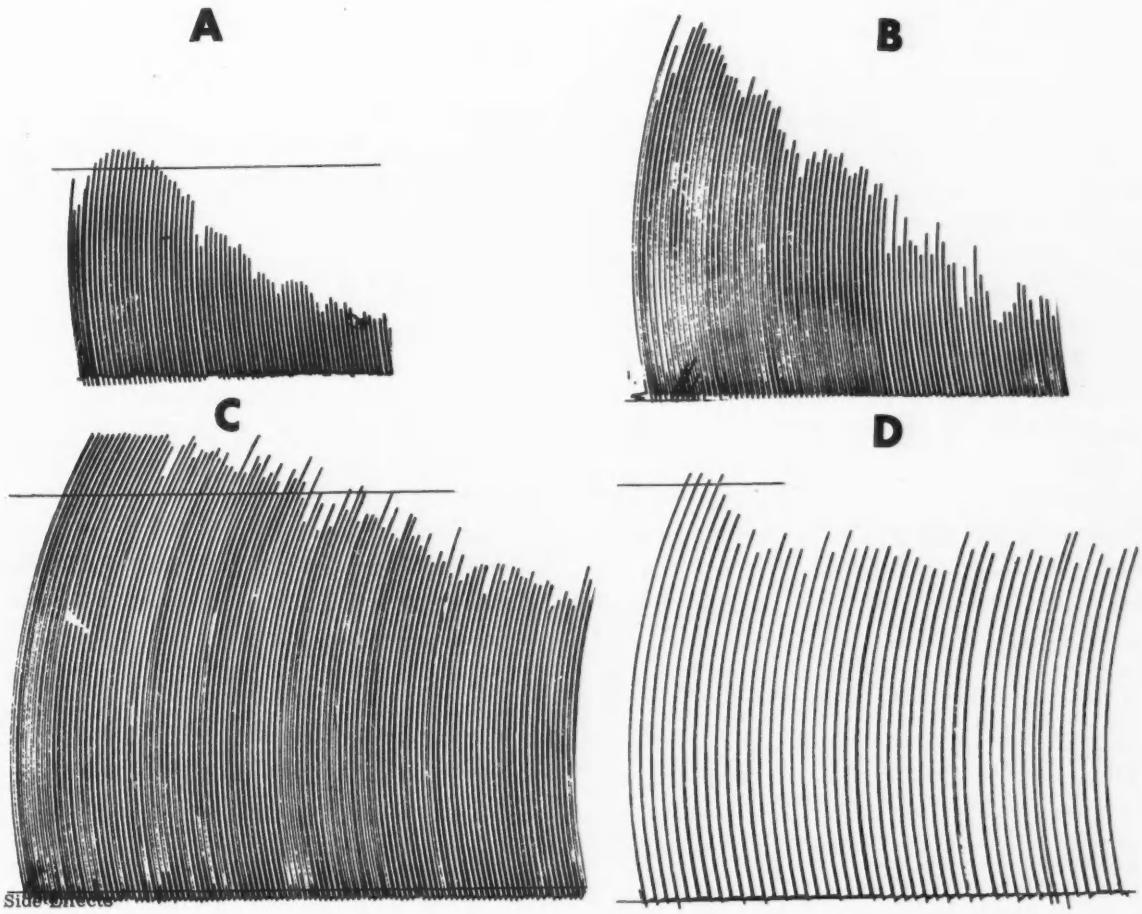

Fig. 1. These are all bulb ergograms. *A* is a bulb ergogram at 1 per second in a patient with myasthenia gravis of moderate severity, off all medication. Note the steady drop in the fatigue curve at 1 squeeze per second.

B, A voluntary ergogram in the same patient when regulated on oral medication and reporting a 65 per cent level of motor activity. There is still a considerable amount of fatigue at 1 per second although there is no question that on medication the ergogram is better than *A*.

D, On this same amount of medication at another time the patient is allowed to squeeze the bulb ergograph with a rest of 8 seconds between squeezes. On this amount of rest there is almost no fatigue in the curve and it resembles the normal one at 1 per second *(C)*.

C, The normal curve of a 51-year-old woman is shown to the left. The bulb ergograph was squeezed at the rate of once per second for a duration of 2 minutes. There is only slight fatigue at the end of this period.

culty can become extremely serious; thus a tenfold recovery time of the diaphragm is incompatible with survival.

We may now turn to the basic problem of transmission at the myoneural junction. The work of Loewi[10] and Dale[11] in identifying a substance similar to acetylcholine in the frog's heart after stimulation of the vagus nerve began the long and controversial explanation of neuromuscular transmission. It is still not fully resolved in spite of hundreds of papers, arguments, and experiments in neurophysiology and pharmacology. There are still some who feel that the essential event is the electric action potential; the chemical changes are secondary to this. The other school, which seems now to be triumphant, and is headed by Nachmansohn,[12] holds that the chemical changes, particularly those involving enzyme cycles with acetylcholine as the essential activator are the critical events with the electrical discharge as a secondary concomitant. Colloquially the two groups are represented by "sparks" and "soup" for the chemical transmitters.

Chemical transmission makes more practical sense than a straight electrical one to me. The action potentials become smaller and smaller in amplitude, and slower in velocity as motor nerve fiber diameter is decreased on its way to its particular muscle. At the terminal points where the fine threadlike branches reach the various motor points of the muscle, the action potential will be of very small amplitude and have a relatively sluggish velocity. It is difficult to see how such attenuated and diminishing electrical events could by themselves get across these tiny gaps and stimulate the muscle into sustained and reliable activity without some help. The critical part of the transmission of the signal from the alpha motor cell in the anterior horn of the spinal cord to the muscle cell is *the bridging of this tiny myoneural gap.* It is the only spatial break in the continuity of the motor nerve-muscle system. Granted that where the fiber diameter is large the large initial neural impulse can move by purely electrical spread, how can such an attenuated voltage of the terminal fiber jump any gap at all, even a minute one? The concept of chemical transmission is, therefore, a logical one, and the transmitting substance as it is formed at the terminal branch of the nerve would act as an amplifier or catalyst in making the final physiologic activity more certain. At any rate, we are now sure that acetylcholine is the transmitter of the myoneural junction and activator of the motor end plate of the muscle. It may also be essential in the billions of synapses in the spinal cord and brain itself.

The concept of chemical mediators requires a series of balanced equilibria that work in a cycle which is vulnerable to the presence of excesses in the various chemicals involved and which may reverse or stop the smooth and efficient chemical cycle from continuing. In natural processes involving chemical mediators a certain amount of waste is obvious. This is typical of nature; thus, in order to make certain of the fertilization of an ovum many millions of spermatozoa are produced. At the terminal end plate of the motor nerve the formation or ejection of the quanta of acetylcholine molecules must be in excess of the few that are required to depolarize the minute receptor membrane or end plate on the muscle fiber. Fatt[13] first showed the resting motor nerve ending is continually "squirting" or "oozing" out small quanta of acetylcholine. These are not enough to "fire" the end plate but may help maintain its special sensitive property that is not found anywhere else in the muscle fiber. When the motor nerve ending fails to produce this resting acetylcholine, as in denervation from cutting the nerve, the end plate's specific properties eventually disappear. Even though the distance between the terminal nerve bouton and the receiving end plate on the muscle is ultramicroscopic (200 Ångström units) according to Lehrer,[14] the dispersion of molecular substances which would move about by diffusion in all directions is obviously wasteful in this respect and many molecules will be

left that are not attached to the sensitive membrane area. These must be cleaned up also at each cycle.

The normal cycle

The normal cycle in a healthy person or animal as understood today in this chemical system is as follows:

1. The nerve impulse reaches the terminal bouton which then discharges about 100 times the resting quanta of molecules of acetylcholine. A certain number of these molecules reach the sensitive membrane receiving area of the muscle fiber, the end plate, and combine with its structure in a way that is not yet clearly understood. This combination alters the properties of this receptor membrane. Potassium ions move out. Sodium ions move in. The special membrane of the end plate loses its charge of polarization which immediately creates the muscle fiber impulse that rapidly spreads throughout the entire fiber and is associated with a muscular contraction.

2. Cholinesterase which has been concentrated in this area* as a concomitant event associated with these membrane changes now removes by hydrolysis the acetylcholine molecules from the end plate and environs, breaking them into choline and acetic acid. With the sensitive end plate freed of its acetylcholine it can repolarize to a level that permits it once more to receive its acetylcholine and discharge a second time.

3. The choline and acetic acid must now be resynthesized and made once more available as acetylcholine to the bouton of the motor nerve ending. A synthesizing process involving the presence of adenosinetriphosphate and a second enzyme called choline acetylase complete the cycle. Nachmansohn[15] deserves full credit for identifying this final enzyme in 1943.

*Blood levels of cholinesterase bear little if any relation to the concentration of this postsynaptic enzyme, although drugs such as neostigmine reduce both.

The abnormal cycles

Competitive block. In partial *curarization,* as well as in *myasthenia gravis,* the cycle is interfered with by the presence of a molecule which has a greater affinity for the receiving muscle cell end plate membrane than acetylcholine and therefore successfully competes for this minute space and also combines chemically with the membrane. Therefore, the acetylcholine molecules cannot discharge the end plate of the muscle fiber and *chemical transmission* is blocked. This is called competitive block.

Depolarized block. If the second stage of the cycle is interfered with so that the cholinesterase is strongly inhibited or removed, the acetylcholine molecules remain on the receiving membrane area of the end plate of the muscle fiber so that repolarization is impossible and this membrane remains *depolarized.* This also produces a state of complete interference with chemical transmission and is called depolarized block. Substances which, like neostigmine, remove the cholinesterase, chemically produce in the normal muscle fiber this type of depolarized block, which is just as lethal as the competitive block.

Characteristics of myasthenia gravis

The first classical paper on the identification of the dynamics of myasthenia gravis and its relationship to partial curarization was published in 1941 by Harvey and Masland.[16] Recording the electromyogram from the small muscles of the hand as the ulnar nerve at the elbow was stimulated electrically, they had an excellent system in the human to investigate the effect of drugs in myasthenia and in normal subjects. At rates of stimulation of from 1 to 50 per second, in normal individuals, they showed that there was no diminution of the second or subsequent electromyographic responses to the stimulating shock, indicating that the myoneural junction chemical cycle which we have described was exceedingly rapid and efficient. In patients with myasthenia gravis, however, the second discharge was

smaller than the first, and the third, fourth, and fifth became increasingly smaller until there was no response at all. This decline in the electromyogram was a classical finding in myasthenia gravis, and has been used repeatedly by others to identify the disease and study its characteristics pharmacologically. A nearly identical response was obtained when the normal human being was partially curarized with tubocurarine. This led Masland to conclude that myasthenia gravis was some direct form of poisoning with a curare-like substance that pharmacologically and neurophysiologically resembled curare poisoning. Both of these conditions could be restored to what they called a completely normal level by the intra-arterial injection of small amounts of neostigmine methylsulfate so that the effect, reported by Walker[17] seven years before, could now be demonstrated in this exquisitely sensitive human pharmacologic preparation.

As important as this work was at the time, it unintentionally misled many clinicians, including the author, into believing that the correct amount of a suitable anticholinesterase drug would restore each patient to a normal state. Even with the most careful, deliberate, and repetitive juggling of doses of neostigmine we found it quite impossible to restore some of our patients to even half the normal level, and a number died in spite of anticholinesterase treatment. More will be said of this complication of medical treatment later in this communication.

Grob and Johns,[19] working with Harvey in the early fifties with normal subjects and patients with myasthenia gravis, repeated much of the work of Masland, emphasizing the competitive type of block in myasthenia and in curare poisoning. They added, however, critically important data about the other type of block due to excessive cholinesterase depression, the *depolarized block.*

If an anticholinesterase compound such as neostigmine is given to a normal subject, acetylcholine remains in excess at the myoneural junction. The end plate area of the muscle remains depolarized after transmission of the action potential and does not recover so that it can respond again. This depolarized block remains until the cholinesterase builds up once more to release the end plate of the acetylcholine molecules. According to Nachmansohn[20] the inhibition of the esterase from neostigmine slowly reverses as the drug diffuses (reversible inhibition), which is in contrast to the permanent inhibition from the alkyl phosphates which require a chemical like 2 PAM to restore the esterase. If neostigmine is given to a normal person this type of depolarized block always results. To complicate the picture further, in 1956, Grob[21] reported that in normal subjects if intra-arterial acetylcholine was given there was a short increase in the action potential at the muscle followed by a reduction in the height of the discharge in a few seconds, due to the depolarizing block, and some 20 minutes later there was a second reduction in the muscle potential which he felt was due to the presence of one of the breakdown products of acetylcholine, namely, choline. He showed that acetic acid when injected did nothing, but that choline produced a decrease in the second, third, and fourth discharges, similar to the action of curare, suggesting that the mechanism in myasthenia gravis was possibly due to the choline itself.

Churchill-Davidson and Richardson[22] from St. Thomas's Hospital, working with myasthenia gravis patients and normal subjects, showed that the response to decamethonium iodide intravenously was quite different and puzzling. The normal person shows to 2.5 mg. intravenously of this substance an increasing block of the depolarizing type that is aggravated by the injection of anticholinesterase substances such as neostigmine. The myasthenic patient, on the other hand, shows a surprising tolerance to this substance so that 10 mg. intravenously produces no augmentation in the weakness of the patient. If the drug is continued, however, an increase in the

myasthenic weakness then occurs which strangely enough is reversed, partially at least, by the injection of the intravenous neostigmine. This suggests that in myasthenia the end plate response first was that of a depolarizing block, and later showed a competitive block response as acetylcholine does in the normal person. This emphasizes the extreme complexity of the myasthenia process. In subsequent reports Churchill-Davidson[23] stated that this increased tolerance to decamethonium persists in myasthenic patients who go into complete remissions spontaneously, or as the result of thymectomy, and it is also found in a small number of normal persons who do not have clinical myasthenia. This is difficult to explain unless there is a subclinical or latent form of the disorder.

Bennett and Cash[24] reported on the exquisite sensitivity of the patient with myasthenia to curare as a diagnostic test. With one tenth to one twentieth of the curarizing dose marked weakness is brought out in cases of doubtful and suspected myasthenia. Such exceedingly small doses do not affect in any way the normal subject.

In Belgium, Coërs[25,26] has recently worked out a technique for intravital staining at biopsy of a piece of muscle from a myasthenia patient, using a presurgical stimulation and electromyographic test to identify the myasthenic response in that segment of the muscle to be removed. Then the specimen is removed and processed according to his technique. His sections show clearly that the myoneural junction in myasthenia gravis is quite specifically abnormal. Instead of the round bouton of the normal motor ending he finds elongated endings with various curled types of processes not seen in normal subjects or in other abnormal conditions. Various degrees of abnormal forms are seen and others in the same slide will show normal endings. In severe myasthenia nearly half of the endings will be abnormal and in milder cases only 1 in 10. This technique is of great interest to the neuropathologist because in many other diseases such as progressive muscular dystrophy, amyotrophic lateral sclerosis, pathologic muscle or nerve cells are present alongside normal ones, and this scatter of abnormality from extreme levels of involvement through perfectly normal ones is a characteristic finding in diseases of the neuromuscular system. This work of Coërs further helps us understand myasthenia gravis as a more complicated condition than chemical poisoning by a curare-like substance.

The most important clinical difference is that in curare poisoning all of the motor end plates will be uniformly affected by the substance and respond in the generalized manner of pathologic involvement according to the level of the curare given. In myasthenia, on the other hand, the abnormality would be scattered in an unpredictable way in various muscles. In the same muscle there would be normally acting nonmyasthenic terminal motor fibers and severely affected myasthenic ones with abnormal responses. Intermediate levels would, of course, be found. This immediately presents an answer to the tremendous difficulties of pharmacologic balance in adjustment of these patients. Removal of the cholinesterase by anticholinesterases such as neostigmine produces favorable effects or repair, as it is called, in the abnormal myasthenic nerve endings, as shown by Coërs, but the same drug produces a depolarizing block in the remaining normal myoneural junctions. Thus there will be pharmacologic improvement in motor performance in some muscle fibers and early depolarization block in the normal fibers in the same area. It would be expected that, if the ratio of abnormality is about equal to that of normality, the injection of the neostigmine would produce very little improvement in the total power of the muscle. The only reason that usual amounts of neostigmine (1.0 to 1.5 mg. intramuscularly in normal subjects) do not produce clinical signs of weakness in the large muscles of limbs is that the reserve of muscle power is sufficiently large so that weakness would not be apparent from partial depolarized

block. But in any stimulating nerve-to-muscle recording, in which only small units of muscle are examined or in the electronic ergogram, Fig. 2, which we use in our testing, it is clear that in the normal subject, even though not clinically detectable, there is always a decrement in the motor performance when anticholinesterase drugs are used. Therefore, it can be stated categorically that it would be extremely unusual, with a mixed response of this type to a drug, where there are abnormal and normal junctions, to obtain restoration to normal clinical values.

It is of interest to recall Lindsley's[27] early paper (1935) on the electromyogram in myasthenia and to note that he found irregularity of the unit discharge amplitude, a prominent feature. This suggests that some units were normal with no amplitude depression of the action potential. Others were abnormal with marked loss of ampli-

Fig. 2. Comparison of both electronic and bulb ergograms in a patient with myasthenia gravis and psychogenic fatigue.

The left-hand column represents the ergograms before any drug is given. The middle columns are ergograms after 0.6 mg. of atropine intramuscularly. Tests were done 15 minutes after the injection of the atropine. Figures on the right of the illustration are all done 20 minutes after the intramuscular injection of 1.5 mg. of neostigmine methylsulfate.

The two ergograms at the upper left are of an untreated 22-year-old patient with a moderate case of myasthenia gravis. The upper voluntary bulb ergograph was done at a squeeze rate of 1 per second and shows a steady and rapid decrement of the fatigue curve. The last squeeze made under strong urging was no higher than the one preceding it. The ergograph directly below, made about 1 hour later, was at the rate of one squeeze every 4 seconds. There is only slight fatigue in this curve indicating that a period of rest of 4 seconds between each squeeze was of considerable benefit to this particular patient.

On the upper right is the ergogram after the injection of neostigmine at a squeeze rate of 1 per second. Note that the amplitude is higher but there is a steady fatigue curve, just the same, and there is a slight increase about 35 per cent on the last squeeze over the one preceding it, under strong motivation. The curve directly under this was done 20 minutes later at one squeeze every 4 seconds showing again an increase in amplitude, a reduction in fatigue with this period of rest, and very little increase on the last squeeze under strong urging.

The curves marked "Fatigue" *(FAT.)* are the voluntary ergograms of a psychoneurotic patient who complained of being tired all the time. Without medication she showed a steady, decreasing fatigue curve and the last squeeze under strong urging was about 100 per cent greater than the preceding one. The rate of squeezing here was 1 per second. After the injection of atropine sulfate there was an essentially similar curve, and after the injection of 1.5 mg. neostigmine sulfate the curve was not altered significantly, even though the patient had some fasciculations in the tongue and some slight salivation and cramps.

The bottom six curves are electronic ergograms of the left hand. The muscle used was the interosseus muscle of the index finger. The stimulation voltage was 20,000. Duration of the pulse was 7 microseconds. The stimulation rate of the complex was once per second. The fatigue curve of the psychoneurotic patient showed nearly no decrease in amplitude at this rate. There was little change, if any, after the injection of atropine, but after the injection of 1.5 mg. neostigmine methylsulfate there was a marked drop in amplitude and failure of that segment of the dorsal interosseus muscle to move with the stimulating current, showing the presence in the muscle of a considerable amount of depolarizing block from the anticholinesterase injection.

The bottom three electronic ergograms are of the same patient with myasthenia gravis shown in the upper four curves. There is a steady fatigue before medication and there is almost no effect from the atropine, but there is an increase in amplitude and performance after the injection of neostigmine. The weight used in the six electronic ergograph tests was a 4 ounce weight and all stimulations were at 1 per second.

FAT. = Fatigue.

MG. = Myasthenia gravis.

tude, dropping out in some places completely. This fits well with Coërs' findings since he insists on locating with electromyography areas of the muscle which show the myasthenic type of pattern for his special biopsy.

It has been tempting to accept the findings of Walker[28] that the myasthenic muscle produces a curare-like substance which after vigorous use of the muscle reaches the circulating venous blood and can produce increase in myasthenic signs elsewhere in the body. With a tourniquet the venous return of the right upper arm, for example, is obstructed while the muscles of the right hand perform a good amount of work. When the hand is fatigued the tourniquet is released. In a few minutes the appearance of ptosis of the eyes, or weakness in the other hand, suggests the presence of a curare-like substance from the fatigued myasthenic muscles.

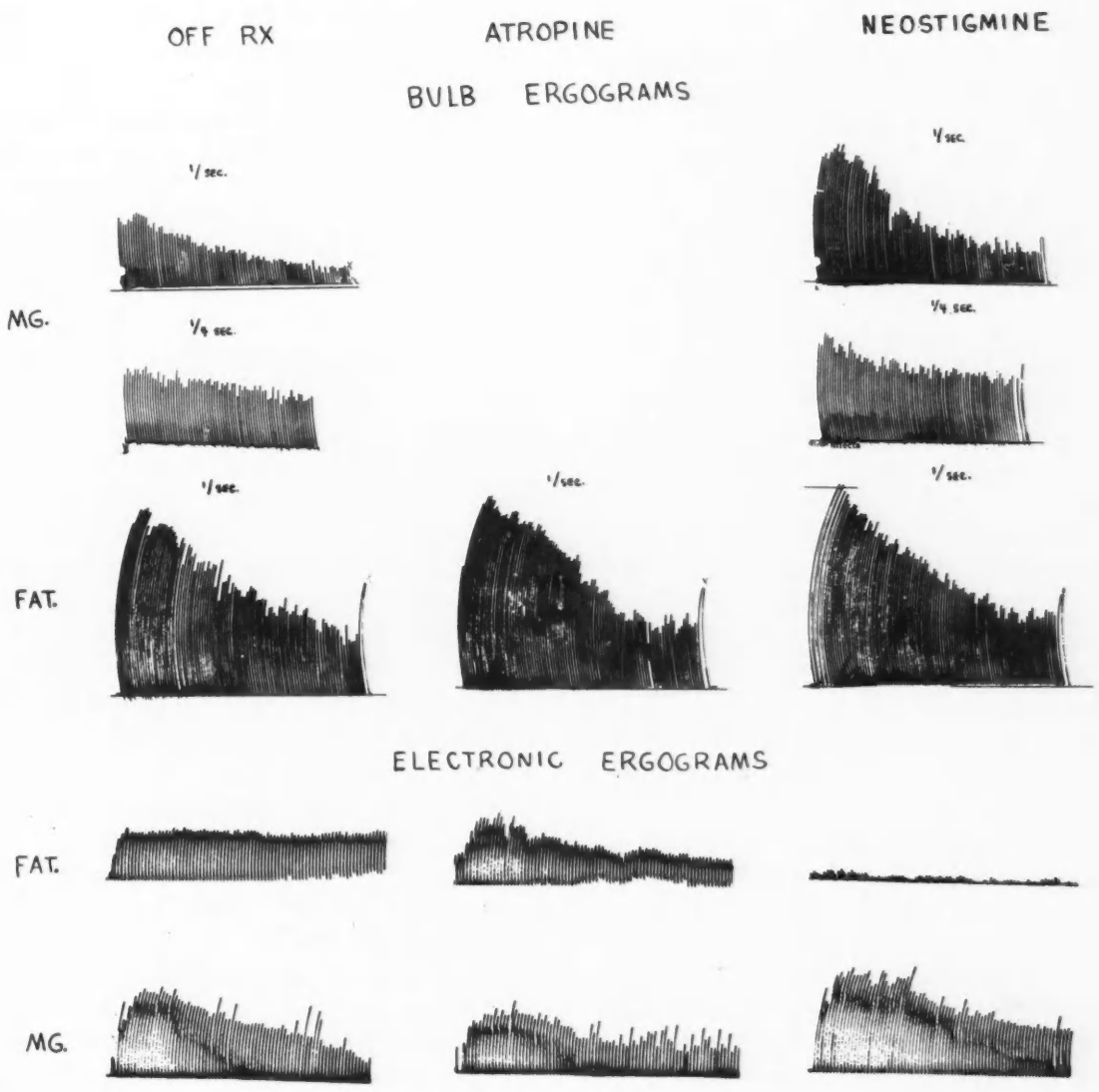

Fig. 2. For legend see opposite page.

Wilson and Stoner,[29] who have made careful investigations of this effect with the ergogram and movies of the eyes, and Grob[30] feel that there is no proof that such a substance exists. Nor does the very careful electrical stimulation of the mouse nerve diaphragm preparation with myasthenic serum by Albrecht Struppler,[31] who showed curare-like depression that disappeared with washing and was not found in normal serum, convince these skeptics. We have been successful in producing the Walker effect clearly on only two occasions. The curare-like substance in the serum of patients with myasthenia may, as Grob suggests, be the residual choline from slow or defective acetylcholine synthesis. If this is the case, there must be a myoneural junction abnormality as well as a biochemical enzyme disorder that varies in its distribution. This surely better fits the clinical features of wide variation and extreme unpredictability of each patient that we see.

Windsor[32] adds further complications to this puzzle by presenting evidence of a cholinergic blocking substance in the serum of myasthenic persons after withdrawal of their regular medicine for 24 hours. Such serum showed no curare effect; only the depolarizing block in the sartorius muscle preparation of the frog. Control human serum had no effect at all.

Treatment

The treatment of myasthenia gravis is largely built up empirically from experience with these *anticholinesterase* compounds. Since the supposed lesion and its relation to the exact nature of the disorder are far from clear at the present time, much that follows will be empirical and from experience. Awareness that the clinical features are never the same in any two cases and that favorable response to a drug may precipitately be followed by bizarre hypersensitiveness or extreme refractoriness will be useful in stressing that successful treatment is both difficult and complicated.

Viets and Schwab[33] have utilized the injection of neostigmine as a diagnostic confirmatory test for myasthenia gravis since 1935. The injection of this drug had no effect on forms of paralysis from involvement of the nerve itself, or in weakness and exhaustion of the muscles as in progressive muscular dystrophy, but had a sharp, consistent, favorable change only in the muscles of myasthenia gravis patients. In the use of this test over these 25 years we have been convinced that in only a small number of cases is it possible to restore for even a few minutes what is called normal function to the affected muscles of the patient with myasthenia. An example will illustrate what is meant here.

A man of 50 presents a picture of complete ptosis on the right, 50 per cent on the left, the right eye is nearly immovable to the sides (less than 10 per cent of normal) and the left moves fully to the right, but not at all to the left. The patient's speech is somewhat nasal and he reports difficulty in swallowing solid food. There is difficulty in getting up out of a chair and with stairs. His grip seems normal. He is given an injection of 1.5 mg. of the anticholinesterase, neostigmine methylsulfate, intramuscularly. Twenty minutes after the injection the right eye is quite open and moves fully to the right and left. The left eye is open 25 per cent more, to 75 per cent, but the weakness in lateral movement is still present. Diplopia is marked. Speech is less nasal but is more difficult, as the tongue seems clumsy. There is excessive buccal saliva, cramps in the abdomen, urgency to urinate, fasciculations in the tongue and lips. There is greater strength with stairs but less power in the grip. There is no doubt that this man has a positive neostigmine test, confirming myasthenia gravis. As a result there are a number of muscles that are nearly normal, some slightly improved, some worse. In this test there is, therefore, evidence of both underdosage and overdosage. There are also a number of undesirable muscarinic effects of the drug on the gastrointestinal tract that

would have been substantially reduced if 0.6 mg. of atropine had been given with the anticholinesterase drug. When this particular group of symptoms, scattered in varying amounts in a variety of muscles, as shown in this particular case, are attacked by oral neostigmine, an even less satisfactory result may be anticipated.

The oral ingestion of neostigmine bromide introduces variables that are beyond the control of the physician, such as different absorption rates due to food in the stomach and intestinal tract. Another variable that is most difficult to anticipate in advance is the amount of exercise and use of the voluntary muscles from hour to hour, to which the patient is subjected during each 24 hour period. The patient who is walking up and down stairs, or carrying bundles, and using his muscles more than normally, would require during this exercise more of the anticholinesterase material in his blood stream. Conversely, if he has to endure an unanticipated long period of inactivity, such as being seated in a bus or automobile for several hours, the amount of the drug in his blood stream might be more than he requires.

In general, mild cases of myasthenia gravis are easier to adjust on oral medication than the more severe ones. An exception to this arises with the so-called ocular type of myasthenia which is considered a mild form of the disorder. The ocular muscles have very little reserve and require much more exquisite balance with the anticholinesterase drug than do the larger muscles in the limbs. Imbalance of the external rectus muscle, for example, which causes diplopia, is much harder to adjust than the levators of the eyelid, which, when weak, produce ptosis. Situations frequently arise where the ptosis can be corrected which makes the diplopia worse. In fact, it is sometimes better for the patient to have the ptosis which closes one eye and eliminates double vision.

Sometimes in ocular cases there is no involvement of the external muscles of the eye such as the lateral rectus, but only ptosis. For reasons that are not at all understood, in some of these patients it is impossible to maintain the eyes open without any ptosis unless one has an excess of the anticholinesterase drug present, so that side effects such as stimulation of the gastrointestinal tract and excessive salivation occur. When such situations are encountered, a nonpharmacologic aid such as a mechanical crutch must be built onto a spectacle frame which can hold the lid up without depending on the muscle power to do so. Intelligent patients soon develop an extraordinary awareness of their drug requirements, so that they can anticipate unusual exercise by taking extra doses of the drug or reducing the drug when they know they are going to have a period of quiet. They learn to recognize the subtle beginnings of excessive medication and, when they appear, to reduce the next dose or postpone taking it until a later time.

Most substances that depress the cholinesterase in the serum have favorable effects on the myasthenic process. The alkyl esters such as DFP, TEPP, and OMPA, with their irreversible and persistent suppression of cholinesterase in the serum and elsewhere, have been tried as pharmacologic agents for the treatment of myasthenia gravis. DFP and TEPP produced so many undesirable side effects that their use was soon given up. OMPA, which is the third of these drugs mentioned, had favorable results in some patients when it was adjusted most carefully and in very small amounts. The amount of cholinesterase suppression, as well as the duration of this suppression, was not as long as that induced by previously mentioned substances. Even here, there were many instances of overdosage which in some cases contributed to the death of the patient in cholinergic crisis. The other more practical objection to OMPA as a therapeutic agent was the difficulty of administration since the ampules of the liquid had to be diluted with water very carefully so that none of the substance reached the skin or sensitive mucous membranes of the patient pre-

paring the mixture. The substance was unstable, and had to be prepared fresh each day. Even though intelligent and sophisticated patients could learn after a while how to do this in a safe manner, another objection that was more decisive was that pharmaceutical manufacturers found its production cost prohibitive. The drug was withdrawn from the market, even though there were a number of patients in each medical center whose disease was well controlled on it, one or two 1 mg. doses of the substance each day giving excellent control of their myasthenia symptoms.

It must be pointed out that OMPA is a volatile liquid quite toxic to the skin and mucous membranes. One of the reasons for its cost is that it is difficult to dispense in ampules. Furthermore the patient must wear rubber gloves while breaking the ampule and must then shake the contents carefully into a glass of water. Only after this does the solution become safe to drink or touch. It must be kept in the refrigerator since it is unstable. Even when kept cold the aqueous solution loses its effectiveness after several weeks. In spite of these risks and difficulties, we found our few patients who benefited from OMPA were eager to continue with it and none reported either skin or mucous membrane burns. We agree with the manufacturer, however, that OMPA was too risky and complicated a product for general distribution.

For example, B. R., a female patient, developed myasthenia at the age of 18 in 1938. There were ptosis, dysphagia, and generalized weakness. She received neostigmine orally and was able to reach a level of approximately 60 per cent of normal on 15 tablets a day. In 1950, at the age of 31, the thymus was removed and she was able to reduce the neostigmine to 10 tablets per day. She was approximately 25 per cent better. Two years later she was able to cut the dosage down to 8 tablets a day. In 1952 she was transferred to OMPA, taking ½ ampule (12.5 mg.) twice a day but no neostigmine. This brought her to nearly 90 per cent of normal. She was able to do all her housework, lead a vigorous life, and only occasionally felt tired. In 1955 when the last ampules of OMPA were distributed to the clinic she had reduced her intake to 1 ampule per week, taking one seventh of an ampule once a day. She was just as strong and normal as ever. Since the drug was no longer available, every other preparation available including pyridostigmin, slow-release neostigmine, slow-release pyridostigmin, ambenonium, and two experimental preparations were all tried as substitutes for the OMPA without producing nearly as good results. Fortunately we were able to supply her with enough of the ampules which will keep indefinitely so that at present she has a 3 year supply. When last seen on Oct. 20, 1959, her condition was 85 per cent of normal, one ampule of OMPA lasting her for 11 days. Obviously she has been in a slowly developing remission since the thymectomy in 1950 and the question that cannot be answered is, "Will she reach this state in its complete form before she runs out of OMPA?"

At the present time there are on the market three substances effective orally in myasthenia gravis. The first is neostigmine bromide tablets (15 mg.). This drug, being the first of the cholinesterase suppressors in use, now has nearly 25 years of clinical experience to support it. Overdosage with neostigmine or Prostigmin, as it is also called, produces very prompt signs of cholinergic stimulation in the gastrointestinal tract, excessive sweating, and salivation. As already pointed out, patients learn to recognize these signs early. To the physician treating myasthenia these muscarinic effects on smooth muscle and glands, also due to cholinesterase suppression, are regarded as undesirable effects of the drug, which is used primarily to improve myoneural transmission. The goal in such treatment is to do this without producing depolarized block on the normal elements of the muscles. The prompt appearance of such signs is a very useful warning that the

top levels of medication have been reached, and this prevents more serious signs and symptoms of overdosage from being encountered from the depolarized block at the muscle end plates.

The second substance was introduced from Europe under the name of pyridostigmin (Mestinon) bromide.[34] It is an analogue of the neostigmine molecule, and in doses of 60 mg. has approximately an effect equivalent to that of 15 mg. of neostigmine bromide. Pyridostigmin bromide produces less stimulation of the gastrointestinal tract when very slight levels of overdosage are reached, so that in patients who do not recognize these early signs, more serious signs of overdosage may develop when this drug is taken by mouth. This has, however, an advantage in that patients who are rather sensitive to neostigmine and, when taking it, cannot reach even a partially efficient therapeutic level without diarrhea, cramps, and excessive secretions, can adjust themselves to pyridostigmin without such untoward effects, and obtain better clinical control of their symptoms.

The third substance, introduced by Schwab[35] in 1954, is ambenonium (Mytelase) chloride, which is a double or bis molecule resembling in its structure two molecules of neostigmine or pyridostigmin linked together in the middle. It has a slightly longer period of action than pyridostigmin and neostigmine, and on reaching slight overdosage levels has less effect on the intestinal tract and secretory apparatus than neostigmine, but is not quite as benign as pyridostigmin. It is more difficult to adjust a patient to ambenonium since it has this longer effect, but a number of patients find that once so adjusted they have a more even and smooth time than when on either neostigmine or pyridostigmin.

On an empiric basis, we recommend that a new patient be started on neostigmine for some weeks in order to find out what his sensitivities and tolerances are, and how the drug works in him. If reasonably efficient control is obtained on neostigmine the drug is continued indefinitely. If, however, undesirable effects occur well before control of the myasthenic symptoms is achieved, it is considered wise to shift the schedule, matching tablet for tablet, to pyridostigmin. If this drug also is not satisfactory then 10 mg. of ambenonium is slowly substituted for each 60 mg. of pyridostigmin. In some patients, it is better to try to achieve a balance of the three drugs by mixing them. For example, some patients might do well with three or four doses each 24 hours of neostigmine, and one or two, or three doses of ambenonium. Pyridostigmin and ambenonium have been combined in this manner, as have ambenonium, pyridostigmin, and neostigmine. We know of 2 patients who have worked out a schedule of all three drugs in a 24 hour period, taking in the morning neostigmine and ambenonium; in the afternoon ambenonium and pyridostigmin; and then neostigmine and pyridostigmin for the rest of the day in alternate doses. It is hard to justify such a complicated mixture of anticholinesterase substances pharmacologically, but in a few cases such mixing seems to work out better than the single drug. One of the troubles with such mixing is that if untoward effects develop, it is difficult to decide which of the drugs is responsible, and here the patients as well as their physicians must be very alert in order to identify the offending substance and reduce its dosage.

One would naturally assume at this point that the way to prevent side effects is, of course, to give an anticholinergic substance like atropine sulfate, regularly throughout the 24 hours in order to diminish or suppress the excessive stimulation of the gastrointestinal tract and the secretory apparatus in the mouth and pharynx. This is hazardous and we feel should be condemned. The only way that a patient can become aware of the level of overmedication is by recognition of the stimulation of the intestinal tract, the excessive salivation, and perspiration. If these are inhibited or buried, so to speak, by the use of anticholinergic drugs, these useful warnings

of overdosage will be completely hidden from the patient as well as from his physician. Neither the patient nor his physician can recognize the early signs of depolarized block of the end plate, which may not be accompanied by fasciculations of the muscles. As the accumulation of the anticholinesterase substances continues, cholinergic block of the myoneural junction begins to assert itself and weakness which soon develops into paralysis ensues. This is the onset of the cholinergic crisis, so-called when a paralysis develops which is frequently more severe than that of the myasthenic process itself. The cholinergic paralysis may not allow even the initial impulses to cross the myoneural junction, since the end plate becomes depolarized without contracting the muscle, so that there may be complete inability to perform muscular movement. This involves the respiratory apparatus particularly, with inability to breathe or cough which can, if not arrested promptly, result in death. It is reasonable in a case of overdosage with acute gastrointestinal upset to give a dose of atropine, either by mouth or by injection, to counteract the signs of that single dose. In fact, this is recommended whenever it is necessary but the continued use of anticholinergic drugs is, as mentioned in the previous paragraph, quite another matter.

The technique of balancing the myasthenic symptom with successful oral anticholinesterase therapy and avoiding muscarinic gastrointestinal tract side effects and depolarized block on normal muscles requires the most careful and painstaking individual dosage adjustments. We usually start with 60 mg. a day and increase slowly as indicated until we get the first gastrointestinal signs of overdosage, then reduce the level accordingly. Each period of the day requires special adjustments. At night with sleep reducing muscular activity the dose must be smaller, yet adequate to carry through the 8 hour period. The three-dose slow-release forms of pyridostigmin (180 mg. tablets) are useful in this nocturnal problem. Each patient represents an individual therapeutic challenge.

One patient (M. H.) was adjusted in a few weeks to 8 tablets (120 mg.) of neostigmine bromide per day at the age of 21 in 1937. She has not varied from this amount over the last 24 years although she was married, had a child, was divorced, and finally moved to Europe to live. She still takes the 8 tablets a day and reports that her condition is close to 95 per cent of normal and has been this way since she was originally seen in our clinic in 1937. This patient represents an easy adjustment without variability or change.

M. S., however, at the age of 44 developed myasthenia rather rapidly involving ptosis, dysarthria, dysphagia, and generalized weakness. When she reached a dosage of 12 tablets (180 mg.), of neostigmine per day she had muscarinic symptoms of the gastrointestinal tract. The dosage was reduced one half. Various combinations of neostigmine and pyridostigmin were tried but the patient could reach a level of only 55 per cent of normal. She was close to invalidism and any increase in medication produced disturbance of the gastrointestinal tract. She was hospitalized for 3 weeks and a combination of slow-release pyridostigmin, neostigmine, and ambenonium, and an experimental drug, phospholine iodide, were all tried. As soon as levels were reached that would overcome the myasthenic symptoms severe reactions set in, and she was finally discharged still at a level of not more than 60 per cent of normal. She represented a partial failure of therapy in a most difficult and complicated case, and subsequently died of respiratory infection.

In Mrs. R. Z., aged 55, myasthenia began with generalized weakness and slight diplopia. Within 2 weeks of onset she was stabilized on 8 tablets (120 mg.) of neostigmine a day and reached a level of 90 per cent of normal. She was able to do all her housework without fatigue. Four months later she was able to get along on 6 tablets (90 mg.) a day, and in 8 months

from onset of disease, she was down to one half tablet (7.5 mg.) twice a day. She represents a slowly developing remission in a case which was relatively easy to regulate. It must be pointed out that this patient, who was not educated, was able to effect these reductions in medication herself from the first warnings of side effects from too much medication.

From our survey 25 per cent of patients can be successfully adjusted at an 80 to 95 per cent level of normal muscle function. Another 25 per cent must be content with 60 to 80 per cent of their normal endurance. This allows them to carry on most of their activities and be independent. Another 25 per cent are somewhat handicapped, ranging between 40 and 60 per cent of normal, requiring help and bed rest whenever they are overtaxed or have infections. The remaining 25 per cent of patients are so difficult to regulate on oral medicine that they cannot be improved beyond levels of 10 to 40 per cent.

Problems in treatment of myasthenia gravis

There are a number of clinical states that are encountered in the management of patients with myasthenia gravis which should be mentioned here since they have a specific pharmacologic meaning in relation to therapy. First is the myasthenic crisis. Here a rapidly developing myasthenic process reache levels of interference with respiration a d the ability to cough up the natural secretions formed in the respiratory passages, so that, unless this is treated as an emergency, the patient will die. We have encountered the myasthenic crisis in patients who also have a thymoma. When a patient is unable to handle his secretions, has difficulty in breathing, and other severe signs of myasthenia gravis, it is probably a myasthenic crisis. It must be identified and differentiated from the other type of crisis, the cholinergic one. Here there is ptosis, marked weakness of the extremities, difficulty in holding the jaw open or the head elevated, the voice is typically nasal in quality, and marked dysphagia is present. Breathing is greatly embarrassed and the breath comes in short, difficult gasps. The pupils are dilated, there is an absence of excessive perspiration, and secretions are not conspicuous at this point. Even so, it is not easy to be certain with these signs just mentioned and it is wise here to inject intravenously 1 or 2 mg. of edrophonium (Tensilon). If this drug intensifies any of the symptoms, it indicates the cholinergic crisis. However, if the small intravenous dose of 1 or 2 mg. of edrophonium results in an increase in strength or disappearance of the myasthenic s toms, it indicates a myasthenic crisis. The provement is, to be sure, only transien but the patient will breathe better, the s will be less, his voice will be less nasal, and there will be an increase in strength. There will be an absence of sweating, the pupils will remain large and dilated, and secretions will be handled by swallowing. Here the edrophonium shows that medication is inadequate and immediate increase in neostigmine is indicated. Neostigmine methylsulfate, 0.5 mg., can be injected intramuscularly, or even intravenously. Sometimes heroic measures are called for. These consist of the use of a respirator, and if an airway is not adequate, a tracheotomy should be performed at once. The combination of respirator and tracheostomy may be life saving in the myasthenic crisis, and when needed should be done without hesitation.

The cholinergic crisis must be identified specifically. It is associated with excessive buccal and pharyngeal secretion, marked respiratory embarrassment, breathing with inadequate exchange so that cyanosis is often encountered; the breath comes in short, irregular gasps. The pupils are usually small from the excessive stimulation of the anticholinesterase substance. Fasciculations are seen in the tongue and around the lips, and sometimes n the shoulders and hands. These are *never* encountered in the myasthenic crisis. The patient usually sweats profusely—the so-called cold sweat of the cholinergic crisis. Even so, it is not

always easy to be certain of the type of crisis, and here again 1 or 2 mg. of edrophonium injected intravenously provides the answer. If the secretions and the sweating increase, and the weakness becomes more marked during a period of 2 to 3 minutes, the presence of a cholinergic crisis is confirmed. The appropriate treatment must be instituted at once. This consists of two attacks—a pharmacologic one and a surgical-mechanical one. Where inadequate airway and respiratory exchange are present, the use of a respirator and tracheotomy is indicated as an emergency measure. In addition to this, atropine, sometimes as much as 1 or 2 mg. intravenously, must be given to dry up the secretions and antagonize the excessive cholinergic stimulation of the intestinal tract. These two measures are usually adequate. It is possible by the use of the new oximes developed by Wilson[36] and introduced clinically by Grob[37] and others to restore the cholinesterase to its normal level by giving 0.5 to 1 Gm. of 2 PAM. One must be certain, when dealing with a severe case of myasthenia, that the restoration of the cholinesterase by the use of an oxime does not, by removing all anticholinesterase drug effects, shift the patient from the cholinergic crisis to the myasthenic crisis. If the patient is satisfactorily in a respirator and the tracheotomy is working well, this is not so important, since he can breathe adequately with the mechanical aid.

An example of this type of emergency is illustrated by the case of R. W., a 42-year-old man who had developed mild myasthenia chiefly in the eyes, 2 years previously. The condition responded rather well at first to oral neostigmine. Six months later the disease had progressed rapidly so that he had difficulty with speech and swallowing, but there was little generalized weakness. It was not possible to control these symptoms with neostigmine since it produced undesirable effects in the gastrointestinal tract. X-rays revealed a thymic tumor. Radiation resulted in partial reduction of the tumor. A biopsy indicated that the lesion was an infiltrating one and could not be removed. For the next year, up to the acute phase of his illness in September, 1959, his medication was changed to pyridostigmin, 8 to 10 tablets (0.5 to 0.6 Gm.) a day, and he attained a level of about 50 per cent of normal. The symptoms began to increase in severity from the spring of 1959 until his final admission to the hospital in September. Pyridostigmin was slowly increased and the gastrointestinal symptoms were balanced with tincture of belladonna and paregoric. However, he became weaker and each day or so the medication would produce a "breakthrough" with diarrhea or profuse salivation. When first admitted to the hospital in September he had ptosis, dysphagia, dysarthria, and some increase in salivation but was able to move about his room and make his wants known. Three days after admission, he suddenly had marked difficulty in breathing. When seen 10 minutes later he was unresponsive, cyanotic, the pupils were small, there was excessive perspiration and extreme difficulty in breathing. The intern who had been called, thinking that he was in a myasthenic crisis, was about to give him an injection of neostigmine. However, he was persuaded to withhold this until 1 mg. of edrophonium could be given intravenously. This produced a marked aggravation of the symptoms. At this point an emergency tracheostomy was done, a Bennett respirator was attached, and 1 mg. of atropine sulfate was given intravenously. After 300 mg. of 2 PAM the patient was breathing comfortably in the respirator. This illustrates the danger of trying to neutralize the cholinergic gastrointestinal symptoms of excessive medication and the difficulties for the ordinary physician in the differential diagnosis of the two forms of crises.

There are a number of pharmacologic puzzles not at all clear that appear from time to time in certain patients. The first is the peculiar ratio of oral to parenteral medication with neostigmine. One milligram of the drug intramuscularly, or given slowly over 1 hour intravenously, is roughly equiv-

alent to 30 mg. of the drug by mouth. This varies by about 50 per cent in different patients. The second is the extremely high tolerance reached by some patients to oral dosage without undesirable gastrointestinal effects. For example, a girl of 15 with a severe form of the disease required 120 15 mg. tablets (nearly 2 Gm.) over a 24 hour period. In spite of that she had considerable myasthenia; there was some ptosis and enough weakness to require a respirator at night. Without this unusual amount of drug by mouth severe symptoms that would certainly have killed her developed rapidly. Yet there were *no* secretory or gastrointestinal effects. This dose is well beyond the lethal level for the average human. A few weeks later, after thymectomy, this girl rapidly went into a complete remission which has persisted to the present (9 years). Her daily tolerance went down to 150 mg. per day within 18 days; more than that produced stimulation of the gastrointestinal tract. In two more weeks she required no neostigmine, and has required none for the ensuing 9 years. Others have reported even higher oral daily requirements.* Patients with such huge oral requirements often get along on 20 mg. parenterally, showing even greater oral-to-parenteral ratios than usual.

The third problem is a paradoxical sensitivity to these drugs. This may develop suddenly and without apparent cause in a severe case. It is more usually found directly after thymectomy. Within 24 hours such a patient may develop severe signs of overdosage from one fifth to one tenth the dose of the drug previously tolerated without untoward effects. This does not mean that the myasthenia has disappeared; in fact, the disease may be in exacerbation when this intolerance to the drug develops. It usually means the patient can survive only in a respirator.

For example, a 21-year-old woman with severe myasthenia requiring 1.8 Gm. of pyridostigmin in 24 hours had a thymectomy and was in a respirator for the first 4 hours after the operation because of cholinergic crisis. After no drugs for 24 hours, it was found that even 0.1 mg. of neostigmine intravenously caused excessive secretion and increased the ptosis and hand weakness. Such a dose has no effect on the normal person and is one tenth of what this patient could tolerate without untoward effect before. Such a state usually disappears slowly over a 2 to 3 weeks' period; it did in this case. She is now (3 years later) in a nearly complete remission.

Since we have no evidence that the thymus gland has any active secretion, its removal in myasthenia gravis is purely empiric treatment. About 80 per cent of all thymus glands from patients with this disease examined either after operation or at postmortem show some abnormality. Such abnormalities otherwise occur in less than 1 per cent of cases. The therapeutic benefit of thymectomy in female patients under 40 years of age is clearly positive in 60 per cent of patients, whereas in males it reaches only 25 per cent. Spontaneous remissions do occur, sometimes complete, and sometimes partial, in 18 per cent.

Except for the thymectomy, the only effective therapy in myasthenia gravis has been the use of anticholinesterase drugs. ACTH, vitamins, special diets, endocrine injections, psychotherapy, physiotherapy, and other forms of treatment are without objective benefit in all cases.

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Mechanism of the antihypertensive Effects of diuretics

Possible role of salt in hypertension

The mechanism of the antihypertensive effect of chlorothiazide does not differ from that of such potent salt-depleting therapeutic agents as the mercurial diuretics and the rice diet. The extracellular fluid and plasma volumes are reduced and, as a result, right heart filling pressure, cardiac output, and blood pressure (if abnormally elevated by some pressor stimulus) fall. Because of the reduction in plasma volume, drugs which increase the capacity of the peripheral vasculature, such as ganglioplegic agents, synergize with chlorothiazide. The reasons for some of the contradictory interpretations of chlorothiazide activity are discussed and appear to be due primarily to (1) the difficulty in assessing antihypertensive mechanisms in long-term studies and (2) confusion over the significance of "normal" values for total exchangeable sodium in chronic experiments with chlorothiazide. For the reasons stated, it is suggested that salt plays a permissive rather than a primary etiological role in the genesis of essential hyptertension.

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Clarification of the mechanism of the antihypertensive effects of chlorothiazide and its congeners is of considerable interest and importance. The clinical value of chlorothiazide in hypertension has been demonstrated by its effectiveness in reducing blood pressure particularly when administered in conjunction with other antihypertensive agents.[6,8] The wide margin between effective and toxic doses permits simplified dosage schedules and insures relative freedom from unpleasant side effects.[7] The complicating side action of hypokalemia appears to be manageable with potassium supplementation and the only sensitization reaction of any moment has been an occasional case of dermatitis.

Unlike other antihypertensive agents, chlorothiazide lowers blood pressure exclusively in hypertensive and not in normotensive individuals.[8,30] The selective antihypertensive action raises the question as to whether the drug is a specific antagonist of the etiological factors producing hypertension.[30] The present paper reviews some of the evidence pertaining to the mechanisms

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of the antihypertensive effects of chlorothiazide and concludes that the principal mechanism of the antihypertensive effect is an alteration in reactivity. The alteration appears to be brought about by a change in the pressure-volume relationship of the vascular system and the blood volume which is a consequence of the saluresis.

It has been known for some time that low sodium diets increase the effectiveness of various antihypertensive procedures.[9,27] It also has been a common observation that the diuresis associated with parenteral mercurials could precipitate hypotensive collapse in hypertensive cardiac patients who were taking ganglion-blocking drugs. When it became apparent that oral chlorothiazide approached the diuretic potency of parenteral mercurials it was a natural step to test its value in the treatment of nonedematous hypertensive patients. The results of the preliminary trials, submitted as an abstract to the American Heart Association in June, 1957, indicated that chlorothiazide enhanced the antihypertensive activity not only of ganglion-blocking drugs but also of hydralazine and Veratrum.[9] These clinical observations lead naturally to an examination of the extent of the salt depletion produced by chlorothiazide in nonedematous patients.

Saluretic action in nonedematous patients

Nonedematous, hospitalized, hypertensive patients were placed on a constant daily ration of 4.25 Gm. of salt per day. After the basal daily excretion of urinary electrolytes on this intake was determined, chlorothiazide was administered in a dose of 500 mg. orally 3 times daily. During the first 3 to 4 days after the drug was given, there was an excretion of approximately 250 mEq. of sodium, 400 mEq. of chloride, and 150 mEq. of potassium over and above the basal level of excretion.[8,31,32] Following the initial diuresis the saluretic effect tapered off. Output came back into balance with intake but the deficit was not restored by a period of positive balance. Thus, the initial losses of body stores of sodium and chloride were maintained for at least one to 2 weeks of continuous treatment.[11] The serum concentrations of sodium and chloride remained unchanged. Potassium concentration often fell moderately and this reduction tended to deepen as treatment was continued over a period of months.

Plasma and extracellular fluid depletion

The 250 mEq. of sodium lost from body stores must come either from the cells or interstitial fluids. Total extracellular fluid volume, as estimated by the changes in available thiocyanate space, decreased by about 2 L.[7,31,32] Since body weight declined by an average amount of 1.8 kilograms it was apparent that the extracellular fluid loss could account for the change in body weight without implicating the intracellular fluid volume.[32] Furthermore, since the serum concentration of sodium was essentially unchanged it could be concluded that extracellular isotonicity to sodium was unaltered. The net effect of chlorothiazide administration in nonedematous patients, therefore, is similar to that observed in edematous individuals except that the mobilizable pool of extracellular fluid is considerably smaller in the former. Cellular extraction of potassium also was apparent since the excretion of this electrolyte was above the amount present in 2 L. of extracellular fluid.

Since the interstitial fluid spaces and the plasma volume are in equilibrium, it was not surprising that there was a reduction in the latter, the reduction averaging approximately 350 ml. There also was a corresponding rise in hematocrit reflecting the hemoconcentration.[8,31,32] Similar changes in plasma volume have been observed by others.[4,28]

Relationship between decrease in plasma volume and antihypertensive effects of chlorothiazide

It is well known that depletion of blood volume by even small amounts will enhance

the antihypertensive effects of certain agents, particularly ganglion-blocking agents.[12] For example, in hypertensive patients treated with ganglion-blocking drugs, withdrawal of as little as 2 to 4 per cent of the total blood volume resulted in perceptible additional decrements of arterial pressure.[13] O'Donnell[22] demonstrated a reduction in plasma volume in hypertensive patients treated for several weeks with Kempner's rice and fruit diet. O'Donnell was able to reverse the postural hypotensive effects of the rice diet either by administering salt or else by replenishing the plasma volume with salt-free dextran solutions. It has also been noted that parenteral mercurials (which likewise are potent saluretic agents) increase the responsiveness to antihypertensive drugs; reduce blood pressure in hypertensive patients[17] but not in normotensive

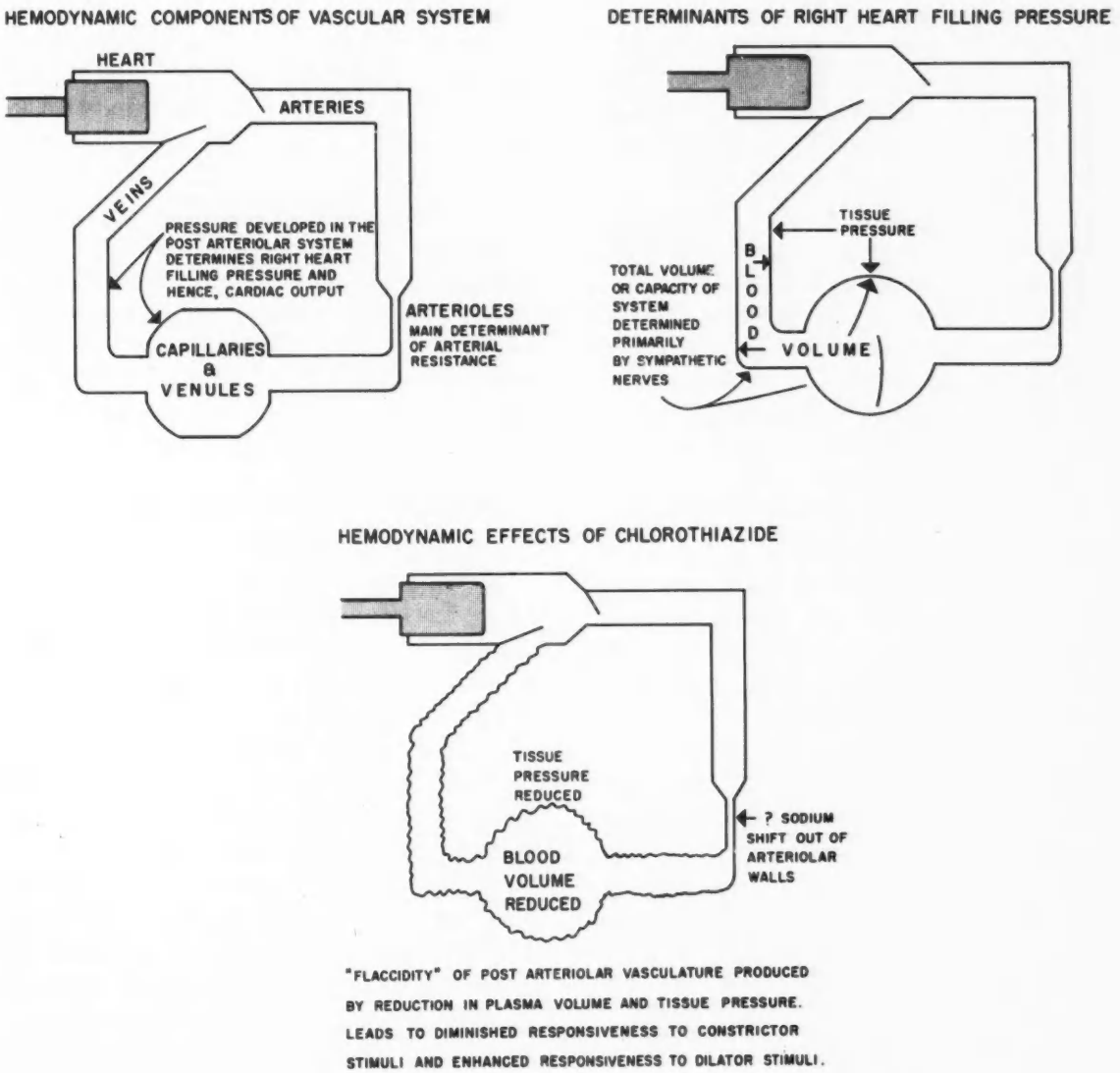

Fig. 1. Schema of proposed concept of the mechanism of the antihypertensive effect of chlorothiazide. Other factors influencing right heart filling pressures and cardiac output, such as myocardial "contractility," pulmonary and systemic peripheral resistance, etc., have been omitted only because they do not pertain to the concept developed in this review. This is not to deny their importance in other circumstances.

subjects[19]; and diminish plasma and extracellular fluid volumes in nonedematous individuals.[19,20] These observations pointed the way for further experiments with chlorothiazide.

If depletion of plasma volume was important in the antihypertensive effect of chlorothiazide, then restoration of the plasma volume should reverse the process. This was indeed the case. Hypertensive patients under hospital control conditions and a constant daily intake of salt exhibited reductions in basal arterial pressure with chlorothiazide alone which averaged approximately 15 per cent less than the pretreatment "mean" $\left(\frac{\text{systolic} + \text{diastolic}}{2}\right)$ blood pressure.[14] When 500 ml. of 6 per cent dextran was infused intravenously over a 15 minute period, the blood pressure rose to approach the pretreatment level.[10,11] Administration of salt was not important in this response as comparable elevations were seen when the dextran was administered either in isotonic saline solution or in 5 per cent glucose in water.[11,32] These observations have been confirmed recently by Dollery and co-workers.[4]

The relationship between the vascular capacity and the contained blood volume seems to be important in this antihypertensive effect. Crosley and his associates[3] have shown and we[11] have confirmed that the hypotensive response to chlorothiazide is associated with a decrease in right heart pressures and in cardiac output as estimated by the Fick principle. Crosley found, in addition, that if the lower extremities were elevated in order to increase the venous return, the cardiac output rose. Dustan and her co-workers[5] using the dye method found a decrease in cardiac output after chlorothiazide. This was reversed by infusion of salt-free dextran.

These observations permit the formulation of a concept of the mechanism of the antihypertensive effects of chlorothiazide and other salt-depleting agents. It is convenient to postulate a labile reserve of total extracellular fluid and plasma volume which are in equilibrium. The amount is approximately 2 L. in nonedematous individuals who have free access to salt in the diet. This reserve of extracellular fluid can be mobilized by severe salt restriction, by potent saluretic agents, or by any event producing dehydration. (It may be noted that drastic purgation, a popular method of treating acute forms of hypertension in bygone days, produces the same effect). The resulting decrease in plasma volume and probably also of tissue pressure impairs the venous return of blood to the heart with a consequent fall in cardiac output and, hence, arterial pressure. Ganglion-blocking drugs also decrease venous filling pressures and cardiac output, but they affect the other member of the relationship between vascular capacity and blood volume. After blocking drugs, the blood volume remains unchanged but the peripheral vascular capacity increases thereby reducing right heart filling pressures.[26] These interrelationships explain the synergism between the hypotensive effects of chlorothiazide and the ganglion-blocking agents.

Effects of chlorothiazide on blood pressure responsiveness

In discussion of the changes produced by chlorothiazide on the effects of pressor and depressor agents, it is preferable to use the terms "blood pressure responsiveness" or simply "reactivity" to "vascular reactivity." The latter phrase implies a change in contractility of the smooth muscle of vascular walls, an interpretation that cannot be assumed on the basis of present evidence.

As previously mentioned, only hypertensive patients exhibit a reduction in basal blood pressure after chlorothiazide alone. Normotensive subjects with basal diastolic levels of 85 mm. Hg or less do not exhibit a significant change in blood pressure following the drug.[8] On the basis of this and other evidence, Wilkins, Hollander, and Chobanian[30] postulated that chlorothiazide and mercurials have a specific antagonistic effect on the etiological factors operative in pro-

ducing hypertension. They proposed that chlorothiazide inhibits the production of renin. Obviously chlorothiazide might provide a pharmacologic tool of some importance in exploring the nature of the difference between hypertensive and normotensive individuals.

As a preliminary to this investigation it was necessary to determine whether chlorothiazide produced a similar depletion of extracellular fluid space and plasma volume in normotensive subjects as in hypertensive patients. Following chlorothiazide in normotensive subjects who were studied under identical hospital conditions, there was an average loss of 285 mEq. of sodium over and above the level of intake during the first few days of therapy.[15] The mean decrease in body weight in these patients also was 2.0 kilograms. This was identical with the weight loss observed in the hypertensive patients. A significant decline in plasma volume was indicated in the normotensive subjects by the fact that the mean hematocrit values rose from 44.2 to 48.3 per cent. Thus, chlorothiazide did not appear to exert a different effect on sodium excretion or fluid volume compartments in normotensive and hypertensive patients.

Although chlorothiazide did not reduce the basal level of blood pressure in normal individuals, it was soon found that their blood pressure responsiveness was altered. The pressor response to agents such as norepinephrine was significantly reduced[21,29] and the depressor response to depressor agents such as trimethaphan was significantly increased.[29] The average elevation of "mean" $\left(\frac{\text{systolic} + \text{diastolic}}{2}\right)$ blood pressure following a given level of infusion of norepinephrine was approximately 15 per cent *less* after, as compared to before, chlorothiazide.[15,29] It is interesting that this is quantitatively similar to the average fall in *basal* blood pressure in hypertensive patients. Reduction in blood pressure responsiveness to pressor agents has also been observed in dogs after chlorothiazide[1] and other diuretic agents.[2]

In order to estimate the importance of plasma volume depletion, salt-free dextran was infused in the chlorothiazide-treated, normotensive subjects. After restoration of plasma volume, the blood pressure responsiveness of these normotensive subjects returned in some cases completely to the control value. Thus, the change in reactivity induced by chlorothiazide seemed to be dependent in large measure on plasma volume depletion.

This observation may explain the differing effects of chlorothiazide on the basal blood pressure of hypertensive and normotensive subjects. If the fall in plasma volume (and possibly tissue pressure) diminishes reactivity to any pressor stimulus, then chlorothiazide also would diminish the response to the unknown pressor agent or agents which produce essential hypertension. Thus, chlorothiazide or any salt-depleting agent reduces blood pressure only when some abnormal hypertensive stimulus is operative. In this respect, its action is nonspecific. Pressor responses of all types are dampened and diminished but not specifically antagonized in the metabolic sense that Wilkins and Hollander[30] proposed.

It is significant that the basal blood pressure was reduced by chlorothiazide in hypertensive patients with diastolic levels as low as 90 mm. Hg.[11] Such results do not support Pickering's[25] thesis that hypertensive patients with only moderate elevations of arterial pressure represent merely the higher ranges of normal blood pressure in the total population. The difference in the response of the basal blood pressure to chlorothiazide when it is above or below 90 mm. Hg suggests that we are dealing with two distinct populations.

Antihypertensive effect of chlorothiazide after long-term treatment

Much of the difference of opinion concerning the mechanism of the antihypertensive effect of chlorothiazide is based on the difference in results obtained in short-term and long-term experiments. After several

months of continuous daily treatment the depletion of total extracellular and plasma volume tends to disappear and after 6 months or one year no significant difference from control values can be found.[32] The reason for this is not clear. For want of a better explanation we have ascribed this to the development of tolerance. In most instances, however, the blood pressure continues to be depressed. This has been the most cogent argument for a specific antihypertensive effect of chlorothiazide distinct from its saluretic action.[30,33] It implies, however, that the drug reduces blood pressure by one mechanism initially and by an entirely different mechanism at a later date.

Another explanation which fits with observations made on the long-term effects of other antihypertensive agents[24] is that the severity of the hypertension decreases after long-term control at lower levels of blood pressure. The reason for this modification of the hypertensive process is not known although there is evidence that the baroreceptor mechanisms can be reset if blood pressure is maintained at a different level for weeks or months.[23] Thus, in order to prove that chlorothiazide still is exerting an antihypertensive effect after long-term treatment, the drug should be withdrawn for some time in order to determine whether the blood pressure will rise to the pretreatment level. In any event, it is difficult to assess the long-term hypotensive mechanisms of antihypertensive agents.

Another discrepancy in the interpretation of the antihypertensive action of chlorothiazide can be traced to a confusion between the estimation of total extracellular fluid space and total exchangeable sodium. The latter provides an estimate of both extracellular and intracellular sodium which can be exchanged with isotopically labeled sodium over a defined period of time, usually 24 hours. The space so measured is considerably larger than the extracellular fluid volume and includes most of the sodium in the body except that which is fixed in bone. In addition, chlorothiazide produces a continuous potassium loss and if the dietary intake of this ion is not ample, a gradual depletion of potassium will occur. Under these circumstances sodium will move into the cells to make up the potassium deficit. Thus, in the studies of Hollander[17] and Winer[33] where total exchangeable sodium was estimated, sporadic results might be expected especially since the experimental measurements were made in outpatients after several weeks or months of treatment. For example, if potassium intake was poor in a given patient, the total extracellular space and plasma volume could be reduced but the value for total exchangeable sodium would be normal because of accumulation of exchangeable sodium in the cells. In addition it is impossible to be certain with outpatients that the prescribed medications are being taken faithfully. It is not too surprising, therefore, that these authors failed to observe a significant correlation between total exchangeable sodium and antihypertensive effect.

Much has been written on the significance of sodium in the genesis of essential hypertension. Most of the valid human evidence on which this supposition is based has to do with antihypertensive effects of salt-depleting procedures. Salt in this situation appears to have no specific etiological significance, however. Its action rather is permissive in that by allowing "normal" expansion of plasma and total extracellular fluid volumes the unknown pressor factors in hypertension can operate more effectively than when these fluid spaces are contracted.

It is entirely possible, of course, that the sodium ion may play an important role in smooth muscle contractility and by this means exert an additional influence in hypertension. However, the data available on this subject are so conflicting that as yet no guiding concepts can be defined.[16] Whatever the role of sodium in vascular reactivity and in hypertension may turn out to be, we cannot neglect the simple relationship of this ion to the maintenance of normal plasma and extracellular fluid volumes and the importance of these to blood pressure responsiveness.

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My suggestions can be summarized in two words: information and regulation; prompt and exact information for the practicing physician from the investigator, the professional societies, the medical journals and the specialty groups, willingness on the part of capable investigators, teachers, and other leaders in medicine to spend time in spreading the truth about drugs; probity and sanity on the part of the manufacturers in keeping advertising factual rather than suggestive, direct rather than irrelevant, truthful rather than misleading; recognition on the part of the practicing physician that his is the final responsibility for the use of a drug and that he cannot give this decision over to anyone else. Regulation there must be for those who will not work from higher motives: regulation by industry to the extent that it can be done; regulation by organizations of physicians where they can help, and regulation by government where the others fail to do the work. Let those who object to the third alternative strengthen the first two.

These things should be done; those things can be done; shall we here agree that these things will be done? In the words of George Washington, "Let us raise a standard to which the wise and just can repair."

FROM "TWIXT THE CUP AND THE LIP," BY HARRY F. DOWLING, A.M.A. ARCHIVES OF INTERNAL MEDICINE, VOL. 100, P. 534, OCTOBER, 1957.

The pharmacology of neuromuscular blocking agents in man

Because of great species variation in the effects of neuromuscular blocking agents, the results are often not applicable to man. Although the subject has been very extensively studied in experimental animals, the necessity has been pointed out for determining the actions of these drugs in man as well. Symposia have been held and monographs written, but this is the first attempt to review the entire literature of the pharmacology of the muscle relaxants in man.

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The pharmacology of neuromuscular blocking agents has been studied extensively in laboratory animals and has been the subject of numerous publications. Because of the large quantitative and qualitative species variation in the neuromuscular and other effects of relaxants,[125,303,406] the results of animal experiments are frequently not applicable to man and it has been emphasized repeatedly that their pharmacologic actions should be studied in human subjects.[124,304,376,382] Considerable information is available on the human pharmacology of neuromuscular blocking agents in monographs[124,331] and symposia,[321,368] but so far no attempt has been made to review in a single publication the literature on the human pharmacology of muscle relaxants.

In the following pages an attempt will be made to correlate the pharmacologic effects of neuromuscular blocking agents with their safe and efficient clinical administration. This survey will deal primarily with the quaternary ammonium type myoneural blocking agents and, of these, only those compounds will be discussed which have been widely used clinically or the study of which serves to emphasize basic principles of the human pharmacology of relaxants.

The list of neuromuscular blocking agents to be reviewed is presented in Table I.

Limitations inherent in the pharmacologic study of any drug in human subjects have also influenced the investigation of neuromuscular blocking agents. Thus, little or no information is available on their acute and chronic toxicity in man and, with few exceptions, all observations were made in the intact organism, instead of on isolated nerve-muscle preparations. On the other hand, in conjunction with their clinical use, there has been ample opportunity to observe the influence of various pathologic conditions and of other drugs on the pharmacologic action of relaxant drugs. Further-

more, from experiments conducted on conscious human subjects, it has also been possible to obtain information on the subjective effects of relaxant drugs.

Most observations on the human pharmacology of relaxants were either coincidental to, or were planned to facilitate, their clinical use. Consequently, while the aspects related to their clinical application have been studied extensively, frequently little information is available on many other aspects of considerable interest to pharmacologists. It has been attempted to include only primarily quantitative data in this review, but occasionally, in order to complete the picture, it is necessary to utilize semiquantitative observations and even clinical impressions. It is hoped that, if it serves no other purpose, this review of the various pharmacologic effects of relaxant drugs in man will stimulate further systematic research in this important, but relatively undeveloped, field.

I. Neuromuscular transmission and neuromuscular block in man

A. Neuromuscular transmission. Many aspects of the mechanism of neuromuscular transmission are still controversial. Our knowledge of this process is especially hampered by the lack of information at the molecular level.[369] The most widely accepted concept of the mechanism of neuromuscular transmission, based on the work of Nachmansohn[291] and his associates,[401] has been discussed elsewhere,[124,174] and will only be summarized briefly.

When a nerve impulse reaches the neuromuscular junction, acetylcholine (ACh) is liberated and becomes adsorbed to the cholinergic receptors of the end plate. Because of this, the permeability of the end plate for Na^+ and K^+ changes temporarily and the end plate becomes depolarized. This depolarization of the end plate creates the nonpropagated end plate potential.[103] After the magnitude of the end plate potential reaches about 45 millivolts, it overcomes the resistance of the surrounding muscle membrane and becomes the propagated action potential, which after a lag of 2 to 3 milliseconds initiates contraction of the muscle fiber.[292] By the time the muscle fiber is fully contracted, the ACh has been attracted from the cholinergic receptors to the acetylcholine esterase (AChE) present at the end plate and is hydrolyzed to acetic acid and choline, the end plate has become repolarized and is ready for the next nerve impulse. In other words, neuromuscular transmission is dependent on a depolarization-repolarization sequence.

B. Neuromuscular block. Interference with either the depolarization or repolarization phase of neuromuscular transmission may produce neuromuscular block, the various causes of which have been discussed elsewhere.[61,124,174] Since this review deals primarily with the pharmacologic effects of quaternary ammonium type neuromuscular blocking agents, only the block produced by these agents in man will be considered.

It was originally believed that the quaternary ammonium type neuromuscular blocking agents, depending on their molecular structure,[37] produce either a nondepolarization[121] or a depolarization block.[52] The nondepolarization block caused by the relatively bulky pachycurares,[37] e.g., d-tubocurarine (d-Tc), has stable characteristics, not influenced by the duration of its administration. The block is not preceded by signs of stimulation, it is antagonized by anticholinesterases,[2] depolarizing relaxants,[187] K^+,[227] and cold.[407] Variation in individual reaction to the effects of identical doses* in unanesthetized human subjects is less than with depolarizing relaxants[135] and they affect grip strength much more than vital capacity.[135,381]

The characteristics of the depolarization block caused by the relatively slender leptocurares[37] are more variable and depend on the duration of their administration.[149] The neuromuscular block is usually preceded by signs of stimulation. These can

*In terms of milligrams per kilogram of body weight.

Table I. *Neuromuscular blocking agents discussed*

Generic name	*Trade name*	*Abbreviation used*	*Molecular weight of*		*Weight of cation expressed as per cent of salt*
			Salt	*Cation*	
d–Tubocurarine Cl_2 pentahydrate		d–Tc	785.74	624.70	79.5
Dimethyl tubocurarine Cl_2	Mecostrin	dim Tc Cl_2	723.72	652.80	90.5
Dimethyl tubocurarine I_2	Metubine	dim Tc I_2	906.64	652.80	72.0
C–toxiferine I*		Toxiferine	685.70	614.78	89.5
C–curarine I*		Curarine	667.70	596.78	89.5
Gallamine triethiodide	Flaxedil		891.56	510.90	57.3
Benzoquinonium Cl_2	Mytolon		617.70	546.80	88.5
Laudexium methylsulfate	Laudolissin		1077.33	855.13	79.0
Decamethonium Br_2	Syncurine	C10	329.48	258.56	78.5
Succinylcholine Cl_2	Anectine Scoline	SCh	361.32	290.40	80.5
Succinylcholine I_2	Celocurine	SCh I_2	544.24	290.40	53.5
Suxethonium Br_2	Brevedil E	SECh	478.23	318.40	66.4
Succinylmonocholine I		SMCh	331.15	204.23	61.7
	Imbretil		536.46	376.62	70.2
	Prestonal		678.60	518.77	75.5

*C-toxiferine I and C-curarine I, although not yet adequately investigated in human subjects[152] and used clinically in only relatively few patients,[393] were included in this review for several reasons: (a) they, like d-tubocurarine (d-Tc), are naturally occurring bis-quaternary ammonium compounds; (b) the recent synthesis of C-toxiferine I[25,26] represents a major break-through in organic chemistry; (c) C-toxiferine I is more potent and has a longer duration of action than any other relaxant now in clinical use and might become the long-sought-for agent for the treatment of spastic conditions.

be demonstrated electromyographically,[29,63,178] and are frequently visible after succinylcholine (SCh) and occasionally after other depolarizing relaxants.[189] After a single dose, or short duration of administration in continuous infusion, the block is potentiated by anticholinesterases[137,144,145,150,301,328,374] and by cold.[407,408] The neuromuscular effect is inhibited by the previous[149,266] and antagonized by the subsequent[187] administration of nondepolarizing relaxants. The individual variation in the effects of identical doses* of depolarizing relaxants is greater than that of nondepolarizing agents[135] and, in relation to grip strength, they affect vital capacity more.[135,381] On prolonged administration, however, the characteristics of the depolarization block in man may change.[123,149] The change is gradual and progresses with variable speed in different individuals.[203] Its first manifestation is a gradually decreasing sensitivity (tachyphylaxis) to the effects of repeated identical doses.[201,285,317,318,381] This decreased sensitivity to depolarizing relaxants is accompanied by an increased sensitivity to nondepolarizing agents.[40,123,149] Occasionally, the characteristics of the block induced by depolarizing agents undergo further changes and become very similar to those caused by nondepolarizing relaxants and may be antagonized by anticholinesterases.[117,130,149,199] The type of block produced by depolarizing drugs has been termed biphasic[227] or multiphasic,[205] and its existence has been recently demonstrated on isolated human intercostal nerve-muscle preparation.[341] The second phase block, caused by depolarizing agents, can also be considered a "desensitization" block,[241,377] resulting from the decreased sensitivity of the end plate receptors to the physiologic transmitter, acetylcholine. To what extent the loss of K^+ from the muscle fibers[153,278] contributes to desensitization of the end plate remains to be determined.

*In terms of milligrams per kilogram of body weight.

II. Neuromuscular effects

A. Methods of investigation. The neuromuscular effects of relaxant drugs have

been studied most frequently on anesthetized subjects, but occasionally also on unanesthetized individuals.[31,42,43,63,135,174,189,224,277,290,317] Both methods have certain disadvantages. Many of the general anesthetic agents employed either have an effect of their own on neuromuscular transmission[14,340] or may potentiate[12,139] nondepolarizing or antagonize[374,404] depolarizing relaxants. The main disadvantages in testing muscle relaxants in conscious volunteers have been the small number of subjects used in most investigations, the relatively low doses employed to avoid respiratory paralysis, and the influence of emotional factors.

In most studies the intravenous route of administration was used but on occasion neuromuscular blocking agents were administered intra-arterially,[63,174,189] and also subcutaneously[359] or intramuscularly.[264] Muscle relaxants have also been given sublingually[111] or rectally,[87] but no quantitative studies were made with the last two methods of administration.

Many of the techniques applicable to the assessment of the neuromuscular blocking agents in man have been recently summarized by Mushin and Mapleson.[289]

In conscious subjects, measurement of the grip strength with spring[135,189,381] or mercury[32,184] ergometers, recording of the strength of other voluntary muscles, e.g., finger or foot, or abdominal muscles,[289,290,317] measurement of the twitch response after electrical stimulation of the corresponding nerve,[35,271,317] the vital capacity,[32,135,189,224] tidal volume,[317] or minute volume of respiration,[224] the maximum expiratory pressure,[31] and fluoroscopic observation of the diaphragm[290] have been used to assess the intensity and duration of action of relaxants.

The methods used for the same purpose in anesthetized subjects include the measurement of the twitch response on electrical stimulation of the nerve,[59,186,187,283,374,376] recording of the tidal or minute volume of respiration,[12,113,150,328] observation of the activity of the diaphragm or intercostal muscles by means of pneumographs,[374] or assessment of the inspiratory pressure.[20]

Electromyographic recording of the muscle action potential caused by electrical stimulation of the corresponding nerve has also been employed for the assessment of the effect of muscle relaxants both in conscious[35,63,174,189] and anesthetized[29,61a,119] subjects. An ingenious method was developed by Dillon and his associates[88,340] for the in vitro study of the effects of myoneural blocking agents in human intercostal nerve-muscle preparations. Another technique utilizes fetal phrenic nerve-diaphragm preparations for the same purpose.[54]

There has been considerable discussion on the relative merits of studying the effects of muscle relaxants on voluntary or electrically induced muscle contractions. Opinions also vary as to whether measurement of the force of muscle contractions or recording of the action potentials by electromyography is more suitable for such investigations. The problem has been thoroughly discussed by Poulsen and Hougs[317] and others.[35,63,174,271,374] Since the amplitude of the integrated action potential is proportional to the isometric tension developed by a muscle during voluntary but not during electrically induced contractions,[262] direct measurement of the force of the muscle seems to be more suitable for the assessment of the neuromuscular activity of relaxant drugs.[317] For comparative studies under constant circumstances, however, electromyography can also be employed.[63]

B. Variation in sensitivity to the neuromuscular effects of relaxant drugs. There is considerable individual variation in man in the neuromuscular effects of relaxant drugs and the sensitivity of different muscle groups in the same individual also varies widely.

1. Individual variation. There is a considerable variation in the sensitivity to the neuromuscular effects of identical doses* of the same relaxant between healthy in-

*In terms of milligrams per kilogram of body weight.

dividuals of comparable age, sex, and body build. This variation was encountered with both depolarizing[63,146,183,296,308,317,374] and nondepolarizing[307,308] relaxants. It has been suggested that calculating the dose of relaxant drugs on the basis of the body surface area instead of the body weight results in a more predictable dose-action relationship.[84] Pelikan and associates[307] found a 3 to 4 per cent incidence of increased sensitivity to threshold doses of d-Tc in healthy individuals. With depolarizing relaxants, decreased rather than increased sensitivity is encountered in normal subjects,[146,183] and in unanesthetized young healthy adults, there is greater variation in sensitivity to depolarizing than to nondepolarizing relaxants.[135,308,317]

2. *Variation in sensitivity of various muscles.* It is well known that, if neuromuscular blocking agents are injected slowly or in gradually increasing doses, the intensity of the neuromuscular block will vary with different muscles. According to Bodman,[31] the order of appearance and intensity of the neuromuscular block after d-Tc, gallamine, or laudexium is: oculomotor muscles, muscles of the eyelids, facial muscles, flexors of the fingers, muscles of the tongue and pharynx, muscles of mastication, abdominal muscles, intercostal muscles, larynx, diaphragm. The order of paralysis reported by other observers for d-Tc,[319] decamethonium (C10),[63,173,189] or SCh[135] is about the same.

More detailed investigation on conscious subjects by Poulsen and Hougs[317] revealed that d-Tc and gallamine produced neuromuscular block of greater intensity in the antebrachial muscles than in the flexors of the foot. With C10, the order of the intensity of action was the reverse.

It is generally accepted that the human diaphragm is more resistant to the effects of both nondepolarizing and depolarizing relaxants than any of the other muscles tested. There is a wide variation of opinion, however, on the relative "respiration protecting effect" of the different relaxants, not only in anesthetized subjects in whom, besides the strength of the diaphragm, many other factors may influence respiratory activity, but also in unanesthetized subjects. Usually the introduction of every new relaxant drug into clinical practice was accompanied by claims of superiority regarding its sparing effect on respiration. According to Unna and his coworkers,[381,383] and Foldes and his associates,[135] depolarizing relaxants, in comparison to nondepolarizing agents, have a relatively greater effect on vital capacity than on grip strength. Thus, for example, doses of d-Tc and C10 which produced a 95 per cent reduction in grip strength caused a 31.3 and 61 per cent decrease, respectively, in vital capacity.[383] In contrast, Harvey[189] and Grob[173] and their associates and Poulsen and Hougs[317] found that in comparable doses C10 affected respiration less than did d-Tc. The discrepancy regarding the respiration sparing effect of depolarizing and nondepolarizing relaxants may probably be explained by the fact that the observations were usually made on relatively small numbers of subjects. This, together with the great variation in the sensitivity to depolarizing agents, was probably the cause of conflicting conclusions.

Despite the undoubtedly greater relative respiratory depressant effect of depolarizing drugs in conscious subjects, it has been reported that better relaxation can be obtained in anesthetized patients without the complete paralysis of the respiratory muscles with SCh than with the long-acting nondepolarizing drugs.[141,374] The explanation of this seemingly contradictory finding is that, with SCh administered in continuous infusion, the concentration of the relaxant can be constantly kept at the steady level, producing the desired degree of neuromuscular block. In contrast, when fractional doses of long-acting relaxants are used, in order to increase duration, the concentration of the relaxants immediately after their intravenous administration is higher than necessary, so that, despite its relatively greater resistance, neuromuscular transmission in the diaphragm is depressed or completely inhibited.

Besides the respiration sparing effect of the relaxant drugs, the most discussed question has been the suitability of any particular relaxant to produce ideal conditions for endotracheal intubation. It has been reported that, when administered in doses capable of producing comparable relaxation of the muscles of the trunk and extremities, d-Tc is more effective than C10 in relaxing the muscles innervated by cranial nerves (face and pharyngeal muscles, muscles of mastication).[173] Foldes and his co-workers[139] also found that, with comparable doses, the relaxation of the jaw was greater and conditions for intubation were better after the use of the nondepolarizing gallamine or benzoquinonium than after the depolarizing C10 or SCh. Despite this, it has been frequently claimed[36,38,129,376] that SCh is the relaxant of choice for endotracheal intubation. This seeming discrepancy can also be explained by the fact that, in general, because of its short duration of action, SCh has been used in comparatively much larger doses than the other clinically employed relaxants. If its enzymatic breakdown is inhibited by hexafluorenium,[137,144,145] 0.2 mg. per kilogram of SCh produces relaxation of comparable intensity and duration to that produced by 0.3 mg. per kilogram of d-Tc, 1.5 mg. per kilogram of gallamine, or 0.07 mg. per kilogram of C10. Despite this, the clinically employed dose of SCh before intubation is 0.6 to 1.5 mg. per kilogram. These doses produce a complete, but short-lasting, paralysis of all muscles and thereby facilitate endotracheal intubation.

C. Potency. The potency of neuromuscular blocking agents may be expressed by the milligrams per kilogram or micromoles per kilogram dose of the quaternary ammonium base or its salt required to obtain partial or just complete inhibition of neuromuscular transmission of nerve impulses to certain muscle groups. The potency can be assayed either in conscious or in anesthetized subjects. In conscious subjects the most frequently used methods are the measurement of the decrease in grip strength or in vital capacity. In anesthetized subjects, the decrease in respiratory tidal volume or the presence of adequate surgical relaxation have been used most often for the assessment of neuromuscular block.

To obtain comparative data on the potency of relaxants, partial inhibition of the same intensity should be produced by the different agents. The production of complete inhibition of neuromuscular transmission is not suitable for comparative studies of potency because it is almost impossible to determine with any degree of accuracy whether the dose used was the "just paralyzing" dose or greater. When assessed in anesthetized subjects, the general anesthetic agent used should be the same and preferably one which in clinical doses has little or no effect on neuromuscular transmission (e.g., thiopental sodium).

Evaluation of the data available on the comparative potency of relaxants is made difficult by the variable experimental conditions and the variety of standards of evaluation used by different investigators. The variation in potency of neuromuscular blocking agents is so great, however, that the data to be presented may be utilized as a guide both for clinical use and for experimental studies on human subjects. Because of the individual variations already discussed, whenever available not only the mean values but also the range of potency will be given.

The effects of increasing doses of relaxants, as with many other drugs, are proportional to the logarithm of the dose. This was demonstrated for the effects of d-Tc, dimethyl-tubocurarine (dim-Tc) and C10 on grip strength,[308] for the effect of SCh on tidal volume of anesthetized subjects,[113] and for the depression of transmission on the isolated human intercostal nerve-muscle preparation[76] by d-Tc.

An excellent survey on the comparative potency of relaxants was compiled by Hoppe.[210] This served as the source of many of the data here presented.

1. In unanesthetized subjects. In unanesthetized subjects, the neuromuscular ef-

Table II. *The effects of neuromuscular blocking agents on the grip strength and vital capacity of unanesthetized subjects*

Agent	*Number of subjects*	*Dose mg./Kg.*	*Per cent reduction of grip strength*	*Per cent reduction of vital capacity*	*Respiration sparing effect**	*Author*
d–Tubocurarine (d–Tc)	1	0.10	84	0	—	Bodman[32]
	10	0.10	78	12	6.5	Foldes et al.[135]
	1	0.12	80	20	4.0	Harvey et al.[189]
	4	0.13	95	31	3.1	Unna et al.[383]
Dimethyl tubocurarine (dim–Tc)	4	0.06	95	16	5.9	Unna et al.[383]
Gallamine	4	0.70	95	20	4.7	Unna et al.[383]
	10	0.70	90	40	2.3	Foldes et al.[135]
Laudexium	1	0.18	88	0	—	Bodman[32]
Decamethonium Br_2 (C10)	10	0.027	54	37	1.5	Foldes et al.[135]
	4	0.03	95	61	1.5	Unna et al.[383]
	1	0.04	100	20	5.0	Harvey et al.[189]
Succinylcholine Cl_2† (SCh)	10	0.08	69	52	1.4	Foldes et al.[135]

*Expressed as the ratio of per cent reduction of grip strength and vital capacity.
†Given 5 minutes after 0.3 mg./Kg. hexafluorenium

fect of relaxant drugs has been usually assayed by the effect on grip strength and vital capacity. The results of these studies are summarized in Table II. The figures of this table indicate that the order of potency of the commonly used relaxants in unanesthetized man is C10> dim-Tc> SCh> d-Tc> laudexium> gallamine. The potency of SCh was determined in subjects in whom its enzymatic hydrolysis was inhibited by hexafluorenium.[135] Because of its fleeting action, the potency of SCh cannot be accurately assessed in the absence of an AChE.

The potency of several neuromuscular blocking agents in decreasing muscle strength by 75 to 100 per cent on electrical stimulation of the nerves and causing less than 30 per cent reduction in tidal volume in unanesthetized subjects determined by Poulsen and Hougs[317] is summarized in Table III.

The head-drop dose of d-Tc and dim-Tc, respectively, was found to be 0.16 and 0.04 mg. per kilogram in a single subject.[274]

All the relaxants investigated had a greater effect on grip strength than on vital capacity. Doses of relaxants which produced a 54 to 100 per cent reduction in grip strength caused a 0 to 61 per cent decrease in vital capacity. As reported by Unna and Pelikan[381] for C10, depolarizing relaxants had a relatively greater effect on vital capacity than comparable doses of nondepolarizing drugs.

Table III. *Doses of neuromuscular blocking agents which cause 75 to 100 per cent decrease in neuromuscular transmission on indirect electrical stimulation (after Poulsen and Hougs*[318]*)*

Agent	*Number of subjects*	*Average dose mg./Kg.*
d-Tubocurarine	16	0.23
Gallamine	13	1.08
Decamethonium Br_2	10	0.053
Succinylcholine I_2	36	0.32
Suxethonium Br_2	9	0.71

2. *Anesthetized subjects.* In anesthetized subjects, the potency of muscle relaxants has been measured by their effect on tidal volume and empirically assessed by the degree of surgical relaxation produced. Both

Table IV. *The effect of neuromuscular blocking agents on the respiratory tidal volume of anesthetized subjects*

Agent	*Number of subjects*	*Dose mg./Kg.*	*Per cent decrease in tidal volume*	*Author*
d–Tubocurarine	6	0.15	0 to 23	Foldes et al. [149]
Gallamine	2	0.75	0	Foldes et al.[149]
Succinylcholine Cl_2	10	0.20*	100	Foldes et al.[145]
	29	0.60	100	Foldes et al.[146]
Succinylcholine I_2	10	0.10	14	Thesleff[374]
	12	0.20	60	Thesleff[374]
	4	0.30	74	Thesleff[374]
	3	0.40	100	Thesleff[374]
Suxethonium Br_2	10	0.40*		Foldes et al.[145]
	29	1.20	100	Foldes et al.[146]
Imbretil	10	0.03	91	Foldes et al.[150]
	10	0.05	100	Foldes et al.[150]
Prestonal	31	1.50	100	Rendell-Baker et al.[328]

*Given 5 minutes after 0.5 mg./Kg. hexafluorenium.

Table V. *The initial dose of neuromuscular blocking agents necessary for the production of adequate surgical relaxation with nitrous oxide-oxygen-barbiturate anesthesia*

Agent	*Number of subjects*	*Dose in milligrams*		*Author*
		Average	*Range*	
d–Tubocurarine	44	17.2	10.0– 30.0	Hunter[219]
Dimethyl tubocurarine I_2	44	8.9	4.0– 18.0	Hunter[219]
C–toxiferine I	27	2.0	0.5– 4.0	Waser and Harbeck[393]
Gallamine	330	77.0	40.0–100.0	Foldes et al.[140]
	24	86.0	50.0–160.0	Hunter[219]
Benzoquinonium	23	9.6	6.0– 15.0	Hunter[219]
	155	12.3	4.5– 18.0	Foldes et al.[138]
Laudexium	100	44.2	——	Dundee et al.[100]
	91	30.0	——	Bodman et al.[33]
Decamethonium Br_2	204	2.4	1.0– 4.0	Foldes and Machaj[128]
	150	3.0	——	Organe[296]
Succinylcholine Cl_2	188	14.0*	8.0– 20.0	Foldes et al.[137]
	>2,000	30.0	10.0– 50.0	Foldes[124]
	546	80.0	——	Bourne et al.[36]
Succinylmonocholine I	10	6.0	5.0– 7.0	Foldes et al.[143]
Imbretil	5	3.5	——	Foldes et al.[150]

*Five minutes after 0.5 mg./Kg. hexafluorenium.

the respiratory tidal volume and surgical relaxation are markedly influenced by numerous factors (e.g., premedication, anesthetic agents, carbon dioxide removal from the anesthetic circuit, type of operation, the surgeon's technique, degree of analgesia, etc.) other than the neuromuscular effect of the relaxants. Consequently, it is even more difficult to obtain reliable quantitative data on the potency of neuromuscular blocking agents in anesthetized than in unanesthetized subjects. These difficulties can be partly eliminated by (a) using the same anesthetic agents and methods in the investigation of all relaxants; (b) determining control values after stabilization of the level of anesthesia; and (c) measuring the effect of the relaxant on tidal volume in the absence of surgical stimuli.[146]

The effect of neuromuscular blocking agents on the tidal volume of anesthetized subjects is summarized in Table IV. The relative sparing effect of nondepolarizing relaxants on respiration is again evident.

The potency of the muscle relaxants based on their ability to produce surgical relaxation is summarized in Table V. The order of potency of the compounds tested was C10> Imbretil> dim-Tc> benzoquinonium> SCh> d-Tc> laudexium> gallamine.

The potency of SCh was also determined in anesthetized subjects by measuring its effect on the twitch tension of fingers produced by electrical stimulation of the nerves.[374] Doses of 0.1 and 0.2 mg. per kilogram of SCh. I_2 produced a 68 and 100 per cent decrease, respectively. The respiratory minute volume decreased after 0.5, 1.0, 1.5, and 2.0 mg. per kilogram of gallamine 18, 46, 71, and 90 per cent, respectively, in a group of patients anesthetized with cyclopropane.[272] The effect of gallamine with ether anesthesia was only slightly greater.

Despite the various methods used by different investigators the data obtained on the relative potency of relaxant drugs in most instances agree. The relative potencies of the muscle relaxants based on their ability to produce surgical relaxation are presented both on a weight basis of their salts and cations and on a molar basis in Table VI.

Table VI. *Comparative potency of neuromuscular blocking agents for the production of surgical relaxation.*

Agent	*On weight basis of*		*On molar basis*
	Cation	*Salt*	
d–Tubocurarine	1.0	1.0	1.0
Dimethyl tubocurarine Cl_2	3.2	3.7	3.4
Dimethyl tubocurarine I_2	3.2	2.9	3.4
Toxiferine	8.5	8.6	7.5
Gallamine	0.3	0.2	0.2
Benzoquinonium	1.0	1.1	0.9
Laudexium	0.5	0.5	0.7
Decamethonium Br_2	7.7	6.0	3.1
Succinylcholine Cl_2	1.6	1.8	0.9
Succinylcholine I_2	1.8	1.2	0.9
Imbretil	5.7	5.0	3.4

When, instead of nitrous oxide and thiopental, general anesthesia is maintained with ether or cyclopropane, the potency of the nondepolarizing relaxants is increased.[124] Thus under ether anesthesia, the potency of d-Tc is tripled[162] and that of gallamine[124] and laudexium[33] is also greater. The potentiating effect of cyclopropane on nondepolarizing relaxants is less marked. Depolarizing relaxants are either not influenced or moderately antagonized by ether.[113,374]

D. Onset and duration of action. Both the onset and duration of action of neuromuscular blocking agents depend on the size of the dose, on the route of administration, and, with the intravenous route, on the speed of their administration. Great variation in these factors, and the fact that the speed of intravenous injection is fre-

quently not stated make the comparison of available data difficult. Since in the vast majority of cases relaxant drugs are given intravenously to human subjects, the onset and duration of their action will be discussed primarily after this route of administration.

1. Onset of action. The effect of the neuromuscular blocking agents on intravenous administration becomes manifest most rapidly (within a few seconds) on the oculomotor muscles,[31] and then gradually on other less sensitive muscle groups. There is no major discrepancy between the development of maximal effect in unanesthetized subjects and in those anesthetized with nitrous oxide, oxygen, and thiopental. The onset of action of SCh and SECh is the most rapid (about 1 minute) and that of benzoquinonium the slowest (6 to 8 minutes). The onset of action of the other compounds tested is about the same (3 to 5 minutes) for each drug. The more rapid onset of action of SCh and SECh is probably due to the fact that, in order to prolong the duration of action of these rapidly hydrolyzed compounds, their initial dose, in comparison to the minimal paralyzing dose, is much greater than that of the other relaxants used. When the hydrolysis of SCh is inhibited by hexafluorenium[137,144,145] and its initial dose* is reduced from 0.6 to 0.08 mg. per kilogram, maximum effect develops in an average of 2.8 instead of 1.0 minutes.[135]

2. Duration of action. The duration of action of the relaxants is influenced by the size of the dose to an even greater extent than is the onset of their action. With comparable doses, the duration of action of C-toxiferine I is the longest (50 to 160 minutes),[393] and that of SECh (1.3 minutes) and SCh (3.0 minutes)[146] the shortest. The order of duration of action of the relaxants in anesthetized subjects is C-toxiferine I> laudexium> C-curarine I> Imbretil> d-Tc> dim-Tc> gallamine> C10> benzoquinonium> Prestonal> SCh> SECh. As already mentioned, inhibition of the hydrolysis of SCh or SECh markedly prolonged their duration of action. Thus 0.08 mg. per kilogram of SCh in unanesthetized subjects had a duration of action of 16.5 minutes.[135] In anesthetized subjects, 0.2 mg. per kilogram of SCh or 0.4 mg. per kilogram of SECh had a duration of action of about 12 to 25 minutes[137] if their enzymatic breakdown was inhibited by hexafluorenium.

E. Effect of repeated doses. There is a marked difference between the neuromuscular effect of repeated doses of nondepolarizing and depolarizing relaxants. The former, even if administered at a time when the first dose has no discernible effect on muscle performance, have much greater effect than the initial dose. This was recognized early by clinicians who first used d-Tc during clinical anesthesia and was also demonstrated on conscious subjects.[308,381,383,384] It was observed that one-half of the initial dose of d-Tc, dim-Tc, or gallamine administered 45 minutes after the first dose produced about the same effect on grip strength and vital capacity as the first dose. Mapleson and Mushin[271] came to the same conclusion on observing the effects of repeated doses of gallamine on the intensity of electrically induced muscle twitch in conscious subjects.

In anesthetized subjects, the administration of a second 1.0 mg. per kilogram dose of gallamine, after respiratory minute volume returned to control values, had a greater and more prolonged effect than the first dose.[12] In agreement with this, the recommended repeat doses of nondepolarizing muscle relaxants during clinical anesthesia are about one-third of the initial dose.[124]

The cumulative action of the long-acting neuromuscular blocking agents, which are excreted partly or wholly unchanged, can be explained by their mechanism of disposal in the human body.[122,235,273] This question will be further considered in the section of this review dealing with the fate of relaxants in man.

*In terms of milligrams per kilogram of body weight.

In contrast, instead of a cumulative effect, tachyphylaxis has been frequently observed after the repeated or prolonged administration of depolarizing muscle relaxants. Unna and his co-workers[308,381,383] found that a second identical dose of C10 administered after 30 minutes was less effective than the first dose. Similarly, Hougs and associates[213] observed that, in conscious subjects, the effects of the continuous infusion of SCh or SECh on voluntary and electrically induced muscle contractions, respiratory tidal volume, and muscle action potential diminished gradually after 60 to 90 minutes.

Similar observations were made on anesthetized subject with C10[217] and SCh [202,207,285] Hunter[217] noted that the intensity of action of a second identical dose of C10 was sometimes less, but the duration was longer, than that of the first dose. Hodges [201,207] observed that the intensity of action of a second identical dose of SCh is less, its onset is slower, but its duration of action is longer, than that of the first dose. Tachyphylaxis to the effects of SCh was also encountered during anesthesia.[94,149] Signs of tachyphylaxis were also observed with Prestonal.[328]

The probable cause of the development of tachyphylaxis to the effects of depolarizing relaxants is a gradually increasing resistance of the end plate to depolarization.[149]

III. Factors which influence the neuromuscular effects of relaxant drugs

The multiplicity of factors that may alter the effects of muscle relaxants have been recently discussed in considerable detail.[125] In the ensuing section, some of the most important factors that influence the effects of relaxants in man will be reviewed briefly.

A. Physical and physicochemical factors.

1. Route of administration. The intra-arterial injection of relaxants results in the most rapid onset, greatest intensity, and usually the longest duration of action. The intra-arterial injection of 10 μg per minute of C10[63] causes a dull ache which reaches its maximum when the paralysis is fully developed and ends 2 minutes after discontinuation of the infusion. The effect of intra-arterial injection of d-Tc and C10 were studied most extensively by Grob and his associates.[174-179] Following the rapid intra-arterial injection of d-Tc, its effect became manifest in 13 seconds and reached maximum intensity in 45 seconds. d-Tc in doses of 0.15, 0.30, 0.60, 0.90 to 1.5 mg. caused, respectively, a 0 to 60, 30 to 60, 30 to 70 per cent reduction of the muscle action potential on the application of a single stimulus. There was a progressive decrease in the successive action potentials when several stimuli were applied 4 milliseconds apart.[178] The quantitative and the qualitative characteristics of the block depended on the size of the intra-arterial dose of C10.[178] A 0.05 mg. dose resulted in a burst of motor activity lasting about 5 seconds. The depressant effect, amounting to 40 to 85 per cent, began in 12 seconds and reached its maximum after 32 seconds. The height of the action potential after the first of a series of stimuli was about the same or only slightly less than after the successive stimuli. After a 0.5 mg. dose, the initial potential was reduced by 95 per cent and the effects became similar to those observed after d-Tc.[178]

With intravenous administration, the onset of action is less rapid and the intensity and duration of the neuromuscular block, due to wider distribution of the relaxant, are less than after intra-arterial injection of comparable doses.

When administered subcutaneously or intramuscularly, 3 to 6 times as much relaxant is necessary to obtain an effect equal in intensity to that caused by intravenous administration. This was shown for d-Tc by Marsh.[274] Holaday[209] used 18 to 24 mg. of d-Tc intramuscularly and obtained good relaxation in 15 minutes. Voorhoeve[389] observed good relaxation without apnea with 1.0 mg. per kilogram of gallamine given intramuscularly in children. Mushin[288] obtained partial curarization with 80 mg. gal-

lamine administered intramuscularly. McDonald and Bryce-Smith[264] administered 1.0 mg. per pound of SCh with hyaluronidase, or 2.0 mg. per pound SCh alone, intramuscularly. With hyaluronidase, the mean period before the onset of apnea was 2.3 minutes, its duration 5 minutes, and the duration of respiratory depression 14.7 minutes. The period before the onset of apnea was 3.7 minutes, its duration 4.8 minutes, and that of the respiratory depression 18.3 minutes, when 2.0 mg. per pound of SCh was administered alone. The method gave satisfactory results in both adults and children. In adults, both the duration of apnea (8.9 minutes) and that of respiratory depression (26.1 minutes) was somewhat longer. SCh was also used subcutaneously in infants and children by Sorenson.[359] Lawson[255] used C10 intramuscularly with hyaluronidase in infants in about 0.1 mg. per kilogram doses. The duration of action of intramuscularly injected d-Tc can be markedly prolonged and its intensity decreased by the use of repository preparations (e.g., Tubadil).[124] When administered in a repository preparation, 0.3 to 1.0 mg. per kilogram doses of d-Tc provide relief of muscle spasm with little or no effect on voluntary movements and muscle strength, although occasionally diplopia and incoordination may be encountered.[261] The plasma level of d-Tc following the administration of 0.5 to 1.0 mg. per kilogram in a repository preparation does not exceed 1 μg per milliliter.[287]

d-Tc was also administered sublingually[294] and per rectum [87,294] in man. The sublingual administration of 2 to 20 mg. d-Tc, [111] or the rectal administration of 150 mg. d-Tc or 800 mg. gallamine [87] produces partial curarization which gives good relief in various spastic conditions.

With intravenous injection, the speed of administration will also influence the intensity of effect of relaxant drugs.[31,319] In general, the faster the injection, the greater the effect—an important fact in comparative studies on the potency of relaxant drugs. Differences in the speed of injection alone may explain the variable results obtained by different investigators after the administration of the same doses of relaxants.

The initial stimulating effect of depolarizing relaxants, frequently seen after SCh, [141,374] and occasionally also after C10,[189, 298,304] is also more marked after rapid intravenous administration. Muscular twitching may be minimized or abolished by slow administration.[141,238,277]

Administration by continuous intravenous infusion instead of repeated fractional doses makes possible the maintenance of a more constant plasma level of the relaxants. Because of this, the degree of muscular relaxation can also be kept more uniform. This method has been used most frequently with SCh[36,80,141,279] and also with SECh.[137]

2. *Duration of administration.* On prolonged administration, the intensity and duration of action of successive fractional doses of nondepolarizing relaxants become progressively greater. This is probably due to the fact that, as suggested by Kalow,[235] the passage of d-Tc and similar substances through the body occurs in three distinct phases. In the first phase, equilibrium between plasma and the extracellular compartment develops fairly rapidly, usually in less than 10 minutes. In the second phase, the drug disappears slowly from the extracellular compartment and is partly excreted or enters sites of destruction. The third phase consists of destruction at these sites, or the slow release from these sites and urinary excretion. The gradual decrease of the amount of relaxant required for the continued maintenance of a neuromuscular block of unchanged intensity probably coincides with the progressive saturation of the tissue reservoirs. This question will be discussed further when the fate of muscle relaxants will be considered.

As already discussed the characteristics of the neuromuscular block induced by depolarizing agents may change gradually in man on prolonged administration and may become similar to the block produced by nondepolarizing relaxants.[40,123,149] This sec-

ond phase of the depolarization block[227] may be antagonized by anticholinesterases.[117,149,199]

3. *Temperature.* Muscle temperature also influences the onset, intensity, and duration of action of neuromuscular blocking agents in both unanesthetized and anesthetized subjects.[408] Cooling has the opposite effect on the neuromuscular block produced by depolarizing and nondepolarizing relaxants. Churchill-Davidson and Richardson[63] observed that cooling slowed the onset and prolonged the duration whereas heating speeded the onset and shortened the duration of action of C10. Reis[327] reported a four- to fivefold increase in the duration of action of Imbretil during hypothermia. Zaimis[407] found that cooling of the muscle potentiated the effects of intravenously or intra-arterially injected SCh and antagonized those of d-Tc in anesthetized subjects. Similarly, it was observed in another series of experiments that cooling delayed the onset, increased the intensity, and prolonged the duration of the neuromuscular effect of SCh.[408]

4. *Hypo- and hyperventilation.* Little information is available in the literature on the influence of hypo- or hyperventilation on the effect of relaxant drugs in man. Dundee[96] compared the quantities of d-Tc required for the maintenance of adequate surgical relaxation during thiopental–nitrous oxide–oxygen anesthesia in patients whose respiration was controlled and in others whose respiration was spontaneous or assisted. Controlled respiration caused an elevation of the blood pH and resulted in an increased d-Tc requirement during the first hour of anesthesia. However, after 2 hours of anesthesia the d-Tc requirements decreased. In patients with assisted or spontaneous respiration, the blood pH decreased. The lower d-Tc requirements in the first hour in the nonhyperventilated group are probably due to the increased ionization and greater potency of this agent at a lower pH.[234] On the other hand, the increased d-Tc requirement during the later stages of anesthesia in hyperventilated subjects might be related to changes in urinary excretion caused by alkalosis.[353]

Carbon dioxide retention due to hypoventilation was also suggested as the possible cause of prolonged postoperative respiratory depression associated with the use of C10,[345] d-Tc,[164] and SCh.[83] On the other hand, the possibility had also been entertained that the effects of controlled respiration on the respiratory center[92] might on occasion cause prolonged postoperative apnea.[147]

B. Physiologic states

1. *Age, sex, and body build.* It has been shown by Hodges[200] that young children, on a body weight basis, are less sensitive to the effects of SCh than adults. A dose of 0.7 mg. per kilogram of SCh, which produced apnea of 0 to 5 minutes' duration in 50 adults, seldom produced apnea of more than 2 minutes' duration in 46 children whose ages ranged from 0 to 10 years. In 27 other children, the mean duration of apnea was 34 seconds; many of them had no apnea and in only one did it exceed 80 seconds. Stead[361] also found that the newborn are resistant to SCh but more sensitive to d-Tc than adults. Unfortunately, his observations were made in infants with intestinal obstruction and probable disturbance of the fluid and electrolyte equilibrium. It is recognized that adults with similar pathologic changes may also be sensitive to muscle relaxants.[124] The increased sensitivity of young children to d-Tc[361] and their decreased sensitivity to SCh[200,361] could not be related to their cholinesterase activity.

Data on the sensitivity of the aged to muscle relaxants are even more scant and controversial. Dundee[97] found no relationship between age and the dose of d-Tc or laudexium required on a body weight basis. Gray[166] reported that aged people were more sensitive and Durrans[101] that they were less sensitive to d-Tc than other patients.

Dundee[97] found no difference between the d-Tc and laudexium requirements of males and females. The influence of body

build on the amount of relaxant required has not yet been investigated. It is a common clinical experience that the greater the ratio of the muscle bulk to body fat, the greater the relaxant requirements[125] on a body weight/dose basis.

Kalow and Gunn[238] also were unable to correlate the effects of SCh with either age or body weight. There was good correlation, however, between the duration of apnea after the intravenous injection of 100 mg. SCh and the plasma cholinesterase level of their subjects. Espinosa and Artusio[113] are of the opinion, however, that the SCh requirement per minute depends on the body weight.

2. Exercise and blood flow. It was observed by Churchill-Davidson and Richardson[63] that in man exercise facilitated recovery after C10-induced neuromuscular block. They attributed this effect of exercise to the increased blood flow associated with it and showed that other factors, e.g., heat and sympathetic block, which also increase blood flow, had similar effect. Mohelsky and Ruben[285] also observed that exercise facilitates recovery after SCh-induced neuromuscular block.

The effect of exercise on the neuromuscular effects of d-Tc gallamine, C10, and SCh has been recently investigated by Foldes and his co-workers.[135] They observed that the time necessary for the return of grip strength to control value was prolonged by exercise after the use of the nondepolarizing d-Tc and gallamine, but was unaffected after C10 or SCh. It therefore seems probable that, besides changes in blood flow, other factors may also be involved in the effect of exercise on neuromuscular block in man. One of these might be the exhaustion of the ACh reserves which would affect more the nondepolarization than the depolarization block. It is of interest that Grob and his associates[178] found similar differences between the effects of repeated electrical stimulation on the muscle action potential in the presence of d-Tc- or C-10-induced neuromuscular block.

C. Pathologic conditions

1. Myasthenia gravis. It is generally accepted that myasthenic subjects are extremely sensitive to the neuromuscular blocking action of nondepolarizing relaxants. This was demonstrated by Bennett and Cash[21] for d-Tc and by Dundee[95] for gallamine. Pelikan and his collaborators[307] found that the mean threshold paralytic dose of d-Tc in 30 myasthenic individuals was 5.42 $\pm$ 4.19 μg per kilogram, as contrasted with 24.77 $\pm$ 10.85 μg per kilogram in 22 normal subjects. Grob,[178] on observing the effects of intra-arterially injected d-Tc on the evoked muscle action potentials, also found that myasthenic muscle is more sensitive to this agent than normal muscle. This was also confirmed by Bergh.[24]

The results reported on the sensitivity of myasthenic subjects to the neuromuscular effects of depolarizing relaxants are less uniform. Sellick[346] and Churchill-Davidson and Richardson[65] observed that myasthenic subjects may be less sensitive to C10 than normal individuals. In contrast, Pelikan[307] found no significant difference in the mean microgram per kilogram threshold dose of C10 in myasthenic subjects (5.53 $\pm$ 3.18) and normal individuals (4.29 $\pm$ 2.80). They observed signs of stimulation in 7 of 25, and an improvement in the symptoms of myasthenia in 13 subjects following the injection of C10, before the development of the neuromuscular block. Injected intra-arterially C10 produced a transient increase in the muscle action potential on electrical stimulation in myasthenic subject.[179] The initial potential of a train was depressed less than in normal subjects, but subsequent potentials were affected to the same extent. The C10-induced neuromuscular block could be reversed by edrophonium or neostigmine.[179] This was first observed in myasthenic subjects by Churchill-Davidson and Richardson,[61,65,66] and later by Pelikan[307] and Bergh.[24] The seemingly controversial observations on the neuromuscular effects of C10 in myasthenia are adequately explained by Churchill-Davidson[61] who found that while the noninvolved mus-

cles may show decreased sensitivity, involved muscles may have normal or increased sensitivity to C10. Bergh[24] also found that C10 may cause profound and prolonged (24 hour) block in the involved muscles of myasthenic subjects. Unanesthetized and anesthetized myasthenic subjects reacted to small (50 μg per kilogram) doses of SCh in the same way as normal individuals.[24]

The increased sensitivity of persons with myasthenia to nondepolarizing and the decreased sensitivity of their noninvolved muscles to depolarizing relaxants suggests that the myasthenic end plate is resistant to depolarizing influences.[64,125,149] This assumption is confirmed by the finding that the myasthenic end plate shows decreased sensitivity to intra-arterial ACh.[1,45,110,177]

Theoretically the increased resistance of the myasthenic end plate to depolarization may be caused by the presence of a curare-like substance,[399,400] or structural changes of the end plate receptors.[125,127] The search for a curare-like substance in the plasma or thymus of myasthenic subjects was unsuccessful[172,251,405] and, with the resolving power of presently available optical and histochemical methods, structural differences in the receptor structure cannot be demonstrated. The possibility cannot be excluded that, instead of a curare-like substance, a depolarizing substance present at the end plate is responsible for its decreased sensitivity to the physiologic transmitter.[127,149] The development of decreased sensitivity to depolarizing and increased sensitivity to nondepolarizing relaxants, similar to those observed in myasthenia, have been observed after the prolonged administration of depolarizing relaxants.[149] Recently a compound, γ-butyrobetaine, capable of producing depolarization block in cats, was extracted from the thymus of a myasthenic subject.[311]

2. *Carcinomatous neuropathy.* Altered sensitivity to the effects of neuromuscular blocking agents has been observed in patients suffering form bronchogenic[7,77,102,191,192,250] and other types[77] of carcinoma. Increased sensitivity to d-Tc and in some of these patients also to C10 and SCh[7] was present. The SCh- or C10-induced neuromuscular block could be reversed by edrophonium. In some[7] but not in all subjects,[102,250] neostigmine improved muscle strength. Clinically many of these patients show similarities to myasthenic individuals. On electromyographic examination, however, findings in the former may differ from those observed in the latter.[102,250]

3. *Liver and kidney disease.* The liver is the main site of synthesis of plasma cholinesterase. In agreement with this, the plasma cholinesterase level decreases in proportion to the severity of the liver involvement.[146] Red cell cholinesterase activity, however, remains at normal levels even in the terminal stages of liver disease. The disposition of SCh in the human organism depends primarily on its hydrolysis by plasma cholinesterase.[132,380] Consequently, the neuromuscular effects of SCh are to a certain extent dependent on the plasma cholinesterase level.[34,114,115,238] This was also demonstrated in patients with liver disease[146] in whom the duration of apnea after a dose of 0.6 mg. per kilogram of SCh was found to be proportional to the plasma cholinesterase level. Neuromuscular block of excessively long duration (prolonged apnea), however, was not encountered in any of these patients, some of whom were in the terminal stages of liver cirrhosis.[146]

Detoxification of d-Tc and dim-Tc occurs, at least in part, in the liver of mammals.[313,386] Despite this, Dundee and Gray[99] reported that patients with liver damage exhibited decreased sensitivity to d-Tc and suggested that the decreased plasma cholinesterase activity may be responsible. In clinical practice, however, patients with advanced liver disease, probably because of their poor physical condition (hypoproteinemia, fluid and electrolyte imbalance) often show increased sensitivity to all types of relaxants.[124]

All muscle relaxants, with the exception of SCh and other ester-type compounds, are excreted partly or wholly unchanged in

the urine.[122] Despite this, unusually prolonged neuromuscular block in the presence of kidney disease can be expected only after the administration of excessive doses. The reason for this is that the termination of action of the nonhydrolyzable relaxants depends primarily on redistribution to inactive tissue depots,[122,235,274] and only after these depots are saturated do urinary excretion and metabolism become the determining factors. Prolongation of the duration of neuromuscular block after the use of gallamine was reported in a female subject whose blood urea level was 200 mg. per 100 ml.

4. Quantitative and qualitative changes in plasma cholinesterase. It has already been mentioned that there is some correlation between the level of plasma cholinesterase and the duration of action of SCh.[114,115,238] This appears, however, to be closer in subjects with abnormally low plasma cholinesterase levels[114,146,206] than in those in whom the plasma cholinesterase activity is within normal limits.[34,146] The intravenous administration of concentrated and purified human plasma cholinesterase (Cholase) shortened the duration of apnea after identical doses of SCh in subjects with normal cholinesterase activity.[32,115] Conversely, selective inhibition of plasma cholinesterase by hexafluorenium caused a marked increase in the intensity and duration of the neuromuscular effects of SCh in both anesthetized.[137,144,145] and unanesthetized[135] subjects. The therapeutic application of Cholase to patients with prolonged SCh-induced apnea, however, was not always successful. Borders and associates[34] found no evidence that the intravenous injection of large doses of Cholase influenced the course of prolonged SCh apnea in anesthetized patients. Lehmann and Simmons,[258] on the other hand, obtained favorable results under similar circumstances in one patient. It has been suggested[125,146,155] that besides quantitative changes in plasma cholinesterase other factors may also influence the neuromuscular actions of SCh. Kalow and Gunn[238,240] encountered several subjects sensitive to SCh in whom not only quantitative but also qualitative changes in plasma cholinesterase could be demonstrated. The plasma cholinesterase of these patients was resistant to the inhibitory effect of dibucaine.

Low plasma cholinesterase activity may be an inherited familial trait.[6,237] Stovner[364] noted that the inhibitory effect of SCh on the hydrolysis of ACh was also decreased in 2 patients who had prolonged apnea after SCh. Foldes and his associates[151] found that the plasma cholinesterase of 2 patients who reacted to normal doses of SCh with unusually prolonged apnea was less inhibited not only by dibucaine and SCh but also by other inhibitors, e.g., neostigmine and Ro2-0683.* In 2 other apparently healthy subjects who reacted similarly to SCh, the plasma cholinesterase activity was both quantitatively and qualitatively within normal limits.[151] The plasma of patients with atypical plasma cholinesterase hydrolyzed SCh in vitro extremely slowly.[151,238] Since excessive prolongation of the neuromuscular effects of SCh can be encountered in seemingly healthy subjects with and without quantitative and qualitative changes in plasma cholinesterase activity, the possibility that other factors may also be responsible cannot be excluded. It has been suggested that abnormal fixation of SCh to the cholinergic receptors of the end plate may be one of the causes of the excessively prolonged apnea occasionally encountered after the use of SCh.[328]

Plasma cholinesterase also hydrolyzes succinylmonocholine, the primary breakdown product of SCh, but at a considerably lower rate.[132] If large doses of SCh are administered to subjects with low plasma cholinesterase and decreased urinary excretion, the neuromuscular effects of succinylmonocholine[143] may prolong the duration of the neuromuscular block.[124,147]

*(2-hydroxy-5-phenylbenzyl) trimethylammonium (bromide) dimethylcarbamate.

5. Disturbances of fluid and electrolyte balance

a. DEHYDRATION. According to Cailar, Baumel, and Durand,[55] dehydration decreases, hyperhydration increases neuromuscular excitability. Besides its direct effect on neuromuscular transmission, dehydration may also increase the intensity and duration of action of relaxants by decreasing the capacity of the extracellular compartment and thereby causing an increase in their concentration[124] in it. The decreased urinary output which usually accompanies dehydration interferes with the urinary excretion of relaxants and thereby also prolongs their effect.[124] Both these points were proved experimentally in normal unanesthetized subjects by Cohen[70] after the intravenous administration of d-Tc. In agreement with this, in clinical practice dehydrated patients are notoriously sensitive to the effects of neuromuscular blocking agents.

b. ELECTROLYTE IMBALANCE. Potassium deficiency especially increases the sensitivity to neuromuscular blocking agents. The influence of various ions has been adequately studied in animals,[125] but unfortunately little or no experimental work has been done on this problem in man. The use of intravenous potassium chloride has been recommended[91,138,221] on an empirical basis to antagonize prolonged neuromuscular block, and this treatment has occasionally proved successful in overcoming prolonged postanesthetic apnea.[141,243] Potassium chloride may be equally effective against the myoneural action of nondepolarizing and depolarizing drugs. Its role in antagonizing nondepolarization block is easily understandable since potassium deficiency is known to antagonize depolarization of the end plate. The antagonistic action of potassium on depolarization block may be due to the replacement of potassium lost from the muscles under the influence of depolarizing drugs.[153,278,404] Another possibility is that, on prolonged administration of depolarizing drugs, the characteristics of the block may become similar to those caused by nondepolarizing drugs[149] and it can therefore be antagonized by potassium. On occasion, prolonged neuromuscular block, induced by either depolarizing or nondepolarizing relaxants, which was previously resistant to antagonism by edrophonium or neostigmine, will become responsive to these agents after the intravenous administration of potassium.

It is possible that, besides potassium deficiency, lack of sodium or calcium or excess of magnesium may also prolong neuromuscular block.[125] Calcium deficiency is most likely to occur in patients who received multiple transfusions of citrated blood.

D. Drugs. Drugs may influence the action of neuromuscular blocking agents by several mechanisms. Many of these are discussed elsewhere.[125] The discussion here will be limited to commonly used therapeutic agents which may be employed deliberately or by coincidence together with muscle relaxants and which may potentiate or antagonize the pharmacologic effects of these compounds. These will be discussed in the order of their clinical importance.

1. Inhalation anesthetic agents. Of the commonly used inhalation anesthetic agents, ether, chloroform, and halothane influence the pharmacologic effects of relaxant drugs most markedly. The effect of cyclopropane is considerably less and that of nitrous oxide and of ethylene in clinically used concentrations is negligible. In general, inhalation anesthetic agents potentiate the neuromuscular effects of nondepolarizing drugs[139]; those of depolarizing compounds are either not affected[139] or are antagonized by ether[374,404] or halothane.[404]

a. ETHER. The potentiating effect of ether on d-Tc in man was first observed by Cullen[78] and confirmed by several others.[12,124,162] It has been suggested that with ether anesthesia the dose of d-Tc should be about one-third of the dose used with thiopental.[124] Ether potentiates dim-Tc to a similar extent.[124] The relaxant dose of gallamine and benzoquinonium can also be decreased by 30 to 40 per cent with ether.[124] Artusio and his co-workers,[12] however, failed to find

any potentiation of the effects of gallamine on the respiratory minute volume by ether. The explanation of this apparent discrepancy may be that only partial neuromuscular block was produced in their subjects which made possible the compensatory activity of the diaphragm. It was noted in unanesthetized volunteers that the tidal volume may remain unchanged and the respiratory minute volume may be increased at a time when the vital capacity is reduced to 20 per cent of control values or less.[135] Ether also potentiates the neuromuscular effects of laudexium.[33,100] Under clinical conditions the neuromuscular effects of C10 and SCh do not seem to be affected by ether.

b. HALOTHANE. Halothane markedly potentiates both the neuromuscular and ganglionic actions of d-Tc.[44,230] It has been reported that in man C10 and SCh are antagonized by halothane.[404]

c. CYCLOPROPANE. The potentiating effect of cyclopropane on the neuromuscular block induced by nondepolarizing relaxants is less marked. With its use, the doses of d-Tc and dim-Tc and of gallamine and benzoquinonium may be reduced by about 40 and 20 per cent, respectively.[124]

2. *Antibiotics.* Of the commonly used antibiotics, neomycin[314,320,341a] and streptomycin[39] both produce a nondepolarization block which is potentiated by ether[314,341a] and can be antagonized by neostigmine.[39, 284,314,341a] Clinically, the neuromuscular effects of neomycin are of great significance. Unfortunately, its neuromuscular effect became known only after severe respiratory depression developed following its intraperitoneal administration during operation in at least 36 patients, several of whom did not recover.[309] The anesthetic agent in most cases was ether and the deaths occurred primarily in infants, young children, and aged individuals. Some of the children received doses of neomycin which would correspond to 3 to 35 Gm. in a 70 kilogram adult.[309] Since neomycin produces a nondepolarization type of block, it should not be used together with nondepolarizing relaxants. Similarly, its use should also be avoided when there is reason to believe that the prolonged administration of a depolarizing relaxant produced a nondepolarization block.[314]

3. *Anticholinesterases.* Besides their antagonistic effects on the neuromuscular block produced by nondepolarizing relaxants and on occasion also by the prolonged administration of depolarizing agents[149] to be discussed later, anticholinesterases also potentiate the neuromuscular effects of depolarizing drugs,[150,301,328] especially those of SCh[137,144,145,374] and SECh.[137,144,145] The potentiation and prolongation of the action of SCh and SECh by hexafluorenium, a selective inhibitor of plasma cholinesterase, was demonstrated both on unanesthetized[135] and anesthetized subjects[144] in whom the combination of SCh or SECh and hexafluorenium was used for the production of surgical relaxation.[10,145] Other anticholinesterases because of their effect on true cholinesterases and their muscarinic side effects are not clinically suitable for the potentiation and prolongation of action of hydrolyzable relaxants.[374]

4. *Concentrated human plasma cholinesterase.* As already discussed, the intravenous injection of concentrated human plasma cholinesterase (Cholase) is capable of shortening the duration of the SCh-induced neuromuscular block in normal individuals.[34,115] Its value, however, in the treatment of prolonged SCh-induced apnea is controversial.[34,258]

5. *Ganglion-blocking agents.* The neuromuscular effects of ganglion-blocking agents and their influence on the activity of relaxant drugs has not been adequately investigated in man. The results of animal experiments indicate, however, that they may be capable of intensifying the neuromuscular effects of relaxant drugs in man as well.[125] In agreement with this, prolongation of the neuromuscular effects of SCh[104, 371] and gallamine[390] was reported after the simultaneous use of these agents and trimethaphan (Arfonad). Eckenhoff[104] observed apnea of 3 hours after the combined

administration of SCh and this agent. Royster and Ditzler[334] advised against the simultaneous use of trimethaphan and relaxant drugs.

6. *Epinephrine and ephedrine.* The multiple effects of epinephrine at the end plate are discussed elsewhere.[125] From the point of view of clinical pharmacology, the possible antagonistic effect of epinephrine and ephedrine on the neuromuscular block produced by nondepolarizing agents or the second-phase block induced by depolarizing drugs is of significance. Because of the fleeting effect of epinephrine, it has been suggested that intramuscular[51] or intravenous[410] ephedrine should be used to potentiate the anatagonistic effect of neostigmine in cases of neostigmine-resistant curarization.[51]

The role of endogenous epinephrine on the effects of neuromuscular blocking agents in conscious subjects is controversial. According to Paton and Zaimis,[304] the excess epinephrine, released by the tension and anxiety associated with such studies, might have antagonized the respiratory effects of d-Tc and augmented those of C10. In contrast to this, Unna and Pelikan[381] feel that the amount of epinephrine released in normal human subjects is insufficient to influence the course of neuromuscular block.

7. *Procaine and other local anesthetic agents.* Procaine can affect neuromuscular transmission by inhibiting the release of ACh at the end plate, by competing with ACh for the cholinergic receptors, by exerting a nonspecific stabilizing action on the postjunctional membrane, and by inhibiting the hydrolysis of ACh by both true and pseudocholinesterase.[125] It also inhibits the enzymatic breakdown of SCh by human plasma cholinesterase.[15,142] In man only the inhibitory effect of procaine and other local anesthetic agents[15] on plasma cholinesterase is of clinical significance. It has been shown that the intravenous injection of 100 mg. procaine potentiated the SCh-induced neuromuscular block in anesthetized man.[142] Because of this, it has been suggested that care should be exercised when hydrolyzable relaxants and local anesthetic agents are used simultaneously during anesthesia.[125,142,258]

8. *Other drugs.* Besides the compounds discussed, there are many more with known effects on the action of relaxant drugs. Only two of these will be considered here briefly.

It has been recently demonstrated by Hodges and his co-workers[207] that the slow intravenous infusion of oxytocin alters the sensitivity of the end plate in man to depolarizing relaxants. They observed that the intravenous infusion of 5 units of oxytocin in 1 to 4 hours abolished the initial stimulating effects of SCh and decreased the intensity and significantly prolonged the duration of the neuromuscular block produced by it. They also found that the serum potassium level was unstable during the intravenous infusion of oxytocin. They suggest that after the continuous infusion of oxytocin, patients may become more sensitive to d-Tc and other nondepolarizing relaxants.

Stovner[365] observed in both unanesthetized and anesthetized subjects that 1.5 to 2.0 mg. per kilogram tetraethylammonium chloride antagonized the neuromuscular effects of d-Tc. He found that partial antagonism to the effects of d-Tc could be completed by the subsequent administration of edrophonium. The administration of tetraethylammonium was accompanied by a moderate (10 to 15 mm.) fall in systolic blood pressure. He suggested that it might be used in conjunction with edrophonium or neostigmine as an antagonist to d-Tc.

E. Interaction of relaxant drugs. In man, neuromuscular blocking agents which produce the same type of block usually have an additive effect.[124] The results of the combined administration of different types of relaxants depend on the sequence and duration of their administration.[94,125]

Even after the termination of any discernible neuromuscular effect of its own, d-Tc affords marked protection against subsequent doses of C10 in both unanesthetized

and anesthetized subjects.[266] Foldes and his co-workers[94,149] observed that after all discernible effects of 0.15 mg. per kilogram of d-Tc or 0.75 mg. per kilogram of gallamine on the respiratory tidal volume of anesthetized subjects has worn off, 3 to 4 times as much C10 or SCh is required to produce respiratory depression as under normal circumstances.[94] The initial stimulating effect of SCh can be abolished by a 5 mg. dose of d-Tc.[286]

The inhibitory effects of nondepolarizing relaxants on the neuromuscular activity of subsequent doses of depolarizing agents was noted by Scurr.[344] Depolarizing neuromuscular blocking agents may also antagonize the effects of nondepolarizing agents.[187,374,404] Thus C10[187] antagonizes the neuromuscular effects of d-Tc and SCh those of both d-Tc and gallamine.[374] The effect of a single dose of C10 or SCh is antagonized by d-Tc.[187] On the other hand, the prolonged administration of C10 or SCh potentiates the action of nondepolarizing drugs like d-Tc or gallamine.[40,149] The clinical significance of the interaction of relaxants will be discussed later.

IV. Other pharmacologic effects of relaxants

A. Effects on the central nervous system. Available information indicates that the intravenous administration of a neuromuscular blocking agent has no effect on the central nervous system of unanesthetized subjects. This was shown not only after the use of relatively small doses, but also after the administration of d-Tc in doses 2.5 times as large as the completely paralyzing dose.[357] No central effects were observed after the intravenous administration of d-Tc, dim-Tc, gallamine, and C10 in doses which produced a 95 per cent decrease in grip strength[381,383] or after comparable doses of SCh.[376] Similar observations were made for d-Tc[244] and for d-Tc, gallamine, C10, and SCh[135] by others. According to Spinelli and his co-workers,[360] however, d-Tc, C10, and SCh administered intravenously also inhibit the synapse between the recurrent fibers and the Renshaw cells in the spinal cord of man.

In the absence of definite electroencephalographic changes after the administration of relaxant drugs in anesthetized patients, it is difficult to assess whether or not they contribute to the central depression. Rees and Davison,[326] using a method described by Pask,[300] failed to demonstrate any effect on the respiratory center by SCh. Despite the absence of any definite proof, Ruben[335] and many other clinicians feel that the combination of paralyzing doses of relaxant drugs and hyperventilation potentiates the central depressant effect of anesthetic drugs. Dundee[96] has shown that when curarized patients are hyperventilated, the quantity of thiopental necessary for the maintenance of anesthesia is less than when assisted respiration is used or the patients breathe spontaneously. In view of this, it is difficult to determine whether the relaxant drug or hyperventilation is responsible for increased central depression.

B. Effects on autonomic nervous system. Most of the information on the autonomic effect of relaxant drugs in man has been obtained during casual observation of variables like pulse rate, blood pressure, electrocardiographic tracings, laryngeal irritability, and reactions to autonomic stimulation. It is assumed that the ganglionic effects of neuromuscular blocking agents depend on competition with ACh at the cholinergic receptors of autonomic ganglia. Some of the relaxant drugs, e.g., benzoquinonium, have a stimulating, others, e.g., d-Tc or gallamine, a depressant effect on ganglionic transmission. The effect of muscle relaxants is not uniform in the various ganglia. Gallamine, for example, depresses primarily ganglionic transmission of the cardiac vagus. Benzoquinonium seems to have selective stimulating action on the pulmonary vagus.

Of the autonomic effects of neuromuscular blocking agents, the depressant effect of gallamine on the cardiac vagus, resulting in elevation of pulse rate and blood pressure, is the most consistent finding,

having been observed in both unanesthetized[135,308] and anesthetized[12,139,140,252] subjects. Although there is no experimental evidence to substantiate this, it has been observed clinically that gallamine depresses the cough reflex[215] and the reflex irritability of the larynx[139] and decreases the incidence of hiccups during upper abdominal surgery.[139] In contrast to gallamine, benzoquinonium has a stimulating effect on the vagus. It causes a marked increase in salivary and bronchial secretions and bradycardia.[11,120,138,139,219] The vagus-stimulating effects of benzoquinonium can be prevented or antagonized by atropine.[11,120]

According to Burstein and associates,[53] d-Tc in clinically used doses inhibits the disturbing autonomic reflexes which occur during anesthesia. They found that the ill effects of carotid sinus, vagal, celiac plexus, pelvolaryngeal, and pelvocardiac reflexes may be prevented by d-Tc. Clark[67] failed to confirm the protective effect of d-Tc on the hyperactive carotid sinus reflex.

The autonomic effects of paralyzing doses of C10[128,189] and SCh[120,376] are negligible. On occasion, however, the reactivity of the sympathetic nervous system to stimulation increases with the use of SCh.[124] The influence of the autonomic effects of neuromuscular blocking agents on circulation will be further discussed in the ensuing section.

C. Circulatory effects. Circulatory changes can be directly caused by the effect neuromuscular blocking agents on the autonomic nervous system or by histamine release.[124] Indirectly, however, many other factors may influence the circulation with the use of relaxants.[248] These include: (1) analgesics or inhalation anesthetics; (2) changes from spontaneous to assisted or manually or mechanically controlled intermittent positive or positive-negative pressure respiration; (3) hypoxia; (4) hypo- and hypercapnia; (5) blood loss; (6) surgical stimuli; (7) reflex stimulation from endotracheal tube; (8) depth of anesthesia. In many publications, it is often difficult to ascertain from the data presented which of these factors was involved in the reported changes. This more than anything else is responsible for the often controversial findings to be summarized.

After the use of d-Tc, no significant changes in pulse rate or blood pressure were observed by some investigators.[12,108,162] Others observed occasional moderate[248,319] or frequent and pronounced[378,398] fall in systolic blood pressure after the use of d-Tc in anesthetized subjects. According to Thomas,[378] the hypotension is proportional to the dose of d-Tc and is greater in debilitated patients. The hypotensive effects of d-Tc were consistent in subjects in whom complete neuromuscular block was produced by the previous infusion of SCh.[107] No electrocardiographic changes were observed after the intravenous injection of 75 mg. of d-Tc.[319]

It is generally acknowledged that gallamine causes acceleration of the pulse rate in both unanesthetized[135,308] and anesthetized subjects.[140,248,252,272] The tachycardia is usually accompanied by moderate elevation of the systolic blood pressure.[140]

With benzoquinonium, the most frequently seen cardiovascular change is bradycardia.[11,120,219] Hunter[219] also noted cardiac irregulatrities with the use of benzoquinonium and Gordon[160] reported profound hypotension in one patient.

Except for a few cases of bradycardia and a single case of paroxysmal tachycardia reported by Guerrier and Mason,[183] the circulatory effects of C10 are negligible.[128]

Reports on the circulatory effects of SCh are perhaps the most controversial. Some observers reported little or no change[56,30,375] in pulse rate or blood pressure after SCh. Moderate increase in pulse rate and blood pressure after clinical doses[3,139] and more marked increase in blood pressure after 1,000 mg. doses[34] were reported by others. Recently several authors reported marked bradycardia, usually after the administration of SCh in relatively large fractional doses.[47,48,259,275,285,311,338,339,352,388,409] Besides bradycardia, hypotension,[56,338,352,409] cardiac irregularities[48,248,337] and transient circulatory collapse,[259]

and asystole[275] were also reported. The bradycardia occurred more frequently during pelvic operations and was assumed to be due to stimulation of the pelvic autonomic system.[339] Since both SCh and succinylmonocholine inhibit the hydrolysis of ACh by both true and pseudo-cholinesterase,[125,148] it is also conceivable that the bradycardia is due to the accumulation of ACh caused by the inhibition of cholinesterase.

More detail on the circulatory effects of relaxant drugs may be obtained from the reviews of Bovet and Bovet-Nitti,[38] Johnstone,[231,232] and Davies.[81]

D. Effects on respiratory system. The respiratory effects of relaxant drugs are primarily caused by their inhibitory effect on respiratory muscles and secondarily by their autonomic effect or histamine-releasing properties which may influence the resistance and compliance of the lungs.

The various claims regarding the sparing effect of one or other muscle relaxant on the respiratory muscles have been discussed in the section of this review which deals with the sensitivity of different muscles to relaxant drugs. In general, it is not possible to achieve adequate surgical relaxation without depression of the activity of respiratory muscles. Consequently, for adequate ventilation, assisted or controlled respiration has to be used. Ventilation may become inadequate, resulting in hypercarbia and hypoxia, even in the presence of seemingly adequate efforts to aid ventilation, if airway resistance markedly increases or lung compliance decreases.

When they develop, these changes are caused in the majority of cases by bronchiolar constriction which can develop in conjunction with the use of relaxant drugs either because of an increase in the vagal tone or because of histamine release. In adequate planes of general anesthesia, this combination is seldom seen in normal subjects. It does occur, however, in asthmatic subjects, in the presence of other allergic manifestations, and occasionally in seemingly normal persons.[82,197,253]

Recent work[248,342] indicates that d-Tc causes little change in lung compliance and airway resistance of normal subjects. Massion and White,[276] however, found a moderate increase in airway resistance in 9 of 12 normal individuals after d-Tc. There was no change in one and a moderate decrease in 2 subjects. The likelihood of encountering bronchiolar constriction with the use of relaxant drugs in sensitive subjects is greatest with d-Tc, laudexium, and benzoquinonium, and least with gallamine.

E. Histamine release. The histamine-releasing properties of muscle relaxants can be studied by the intracutaneous wheal method and may be assessed from the incidence and severity of allergic manifestations, e.g., bronchospasm, urticaria, flushing, and hypotension which may accompany their use. The histamine-releasing properties of d-Tc, dim-Tc, gallamine, and C10 were compared by Sniper[358] after the intracutaneous injection of equipotent doses dissolved in equal volumes. He found that the histamine-liberating properties decreased in the following order: d-Tc = dim-TC> gallamine> C10. Others[43,72,180] also found evidence of histamine release after intracutaneous or intra-arterial injection of d-Tc. Little or no histamine release was observed after the intracutaneous injection of C10[188] or SCh.[375] The histamine-releasing properties of laudexium[32] and Prestonal[170,328] are similar to those of d-Tc. Despite the relatively weak histamine-liberating property of gallamine and SCh, allergic skin manifestations were reported after the use of both.[263,354]

F. Muscle pain. This unwanted side effect of the use of relaxant drugs has been observed only after the use of depolarizing drugs, primarily SCh, and usually in ambulatory patients. It is believed that the muscle pain is associated with the initial stimulating effect of depolarizing relaxants, because, if muscular twitching is prevented by the administration of small doses of nondepolarizing relaxants, the incidence and severity of the postanesthetic muscle pain are diminished.[60,286]

The severity of muscle pain after the use of C10 is low but it has been observed in normal subjects who received C10 for experimental purposes.[61,135] The reported incidence and severity of the muscle pain after SCh is variable. Thesleff[375] and Bourne and co-workers[36] reported slight muscle pain after small doses of SCh in conscious subjects. Churchill-Davidson[60] reported that the incidence of muscle pain is much higher (66 per cent) in outpatients than in hospitalized patients (13.9 per cent). Leatherdale and his associates[256] reported an incidence of 36 per cent of muscle pain in a series of dental patients who were ambulatory within 12 to 24 hours after anesthesia. Morris and Dunn[286] observed muscle pain in 35 per cent of patients who were kept in bed for at least 24 hours after anesthesia on the day of discharge and in 72 per cent seen a few days later in the outpatient clinic. Hegarty[190] found a 25 per cent incidence of muscle pain in hospitalized patients after SCh and none in a comparable group who received other relaxants. In Konow's[247] series, the incidence of postanesthetic muscle pain was about 53 per cent in both out- and inpatients. Mayrhofer[278] found an even higher (89 per cent) incidence of muscle pain after SCh.

Despite the number of reports on postanesthetic muscle pain, it is the experience of most anesthetists that if moderate doses of SCh are administered slowly this complication is seldom encountered in hospitalized patients.[124] Both Adderley[3] and Tewfik[373] found that the incidence and severity of muscle pain after the use of SCh in electroshock therapy are low.

G. Miscellaneous effects

1. Genitourinary effects. With regard to the genitourinary tract, placental transmission of relaxant drugs and their effect on the fetus are of predominant interest. Gray,[162] Whitacre and Fisher,[397] and Prescott[319] state that d-Tc, used in clinical doses, does not pass the placental barrier in concentrations capable of affecting the fetus. Pittinger, Morris, and Keettel,[315] Crawford,[75] and Bianchetti and his co-workers[28] measured the d-Tc content of the fetal blood and found only insignificant quantities. The latter also found only negligible amounts of gallamine in fetal blood. In contrast to this Beck and Nold[18] found that fetal movements ceased after the administration of d-Tc or gallamine to the mother, and returned after the administration of neostigmine. Most observers agree that C10[344] and SCh[79,93,204,246] do not penetrate the placental barrier in sufficient concentration to influence the fetus.

2. Gastrointestinal effects. In clinical doses, neuromuscular blocking agents have little or no effect on intestinal tone and motility. Increased peristalsis was reported with the use of both benzoquinonium[160] and SCh.[339] It was also stated that with the use of SCh the bowels are constricted as during subarachnoid block.

3. Salivation and bronchial secretion. To a variable degree, all the clinically used relaxants cause increased salivation and bronchial secretion. These are most marked after benzoquinonium[124,160] and d-Tc,[162] but were also reported after SCh[81] and other relaxants.

4. Effect on intraocular pressure. Hofmann and Holzer[208] were the first to report that the intravenous injection of SCh caused a rise in the intraocular pressure. This rise amounted to 4 to 8 mm. Hg under thiopental and 10 to 14 mm. Hg under ether anesthesia, and was as high as 18 mm. Hg in unanesthetized subjects. The rise in pressure was accompanied by lateral rotation of the eyeballs. They concluded that it was caused by the contraction of the extraocular muscles. These findings were subsequently confirmed by Lincoff and associates[260] and Dillon and his co-workers,[89] who also attributed the rise in intraocular pressure to contraction or perhaps contracture[260] of the extraocular muscles. Besides the rise in intraocular pressure, SCh also causes enophthalmos.[29a] The retraction of the eyeball in 100 subjects ranged from 0 to 3.25 mm. with a mean value of 2.4 mm. and its duration coincided with that of the apnea.

5. Effect on cholinesterases. The inhibitory effects of neuromuscular blocking agents and their antagonists on human red cell and plasma cholinesterase were investigated by Foldes and collaborators.[125] Of the nondepolarizing relaxants, the inhibitory effects of benzoquinonium on red cell ($I_{50} = 2.2 \times 10^{-7}M$) and that of hexafluorenium on plasma cholinesterase ($I_{50} = 5 \times 10^{-7}M$) were the greatest. Of the depolarizing relaxants, Prestonal inhibited both plasma ($I_{50} = 7.3 \times 10^{-6}M$) and red cell cholinesterase ($I_{50} = 1.0 \times 10^{-5}M$) the most. No correlation was found between the anticholinesterase and neuromuscular effect of relaxant drugs. In contrast, there was a good correlation between the inhibitory effect of these drugs on red cell cholinesterase and the neuromuscular effects of the antagonists of nondepolarizing relaxants. It is of interest that SCh inhibits the hydrolysis of ACh by normal and atypical plasma cholinesterase[237] to different degrees. It was observed by Stovner[364] that SCh inhibited the hydrolysis of ACh by plasmas obtained from patients who reacted to average doses of SCh by prolonged apnea, much less than by those obtained from individuals who reacted normally to this compound. Kalow and Gunn[238] showed that the plasma of subjects in whom SCh causes prolonged apnea does not hydrolyze SCh. Both observations were confirmed by Foldes and his associates.[151]

6. Effect on potassium balance. It was reported that in man, as in other mammals,[245,301] the plasma potassium level may become elevated and the urinary potassium excretion increase after the administration of SCh.[153,278,404] It is generally accepted that the elevation in the serum potassium level and the increased urinary potassium excretion are caused by the release of potassium from the muscles under the influence of SCh.

7. Effect on kidney and liver function and carbohydrate metabolism. There is no evidence that neuromuscular blocking agents have any effect in man on kidney or liver function, or carbohydrate metabolism.[162] Ward and Dance[392] found no significant changes in blood sugar levels in subjects anesthetized with thiopental before and after the administration of SCh.

V. Fate of muscle relaxants

The fate of neuromuscular blocking agents in man will be discussed only briefly. For greater detail, Marsh's publication[274] and the reviews of Foldes[122] and Kalow[235] may be consulted. The distribution of relaxant drugs in man was studied most extensively with d-Tc; data on urinary excretion are available for several other compounds; and, in regard to their breakdown, the most information is available for SCh.

A. Absorption. The absorption of neuromuscular blocking agents from the gastrointestinal tract is slow and incomplete. On rectal administration, 150 mg. d-Tc or 800 mg. gallamine (about 10 times the intravenous paralyzing dose) results only in partial curarization.[87] The absorption seems to be more rapid and complete after sublingual administration.[111]

On subcutaneous or intramuscular administration, 3 to 6 times as much relaxant is required as after intravenous administration to obtain an effect of equal intensity.[264,274,359] With these routes of administration, the onset of the neuromuscular block is delayed by a few minutes and its duration is prolonged. Kalow[233] found that the velocity constant of the diffusion of d-Tc from subcutaneous tissue to blood is considerably greater than that from blood to the tissues.

B. Distribution. After rapid intravenous administration, the plasma concentration of d-Tc approaches the theoretical maximum, calculated on the basis of plasma volume.[71, 235,274] Muscle relaxants, like other quaternary ammonium compounds, usually do not penetrate cell membranes[46] and cannot be demonstrated inside red cells.[71,274] d-Tc[5] and presumably other relaxants can be directly bound to plasma proteins (albumin and γ-globulin). The plasma concentration of d-Tc falls, at first rapidly, and then con-

siderably more slowly, for several hours. Thus it was shown that after the intravenous injection of 0.22 mg. per kilogram of d-Tc to unanesthetized subjects 40, 60, and 75 per cent disappeared from the plasma in 10, 20, and 60 minutes, respectively.[71]

The initial rapid fall in the plasma level of d-Tc and other relaxant drugs is primarily due to diffusion into other parts of the extracellular compartment.[122,233,274] Comparison of the course of the neuromuscular block with the plasma levels of d-Tc indicates that the rate of diffusion into various parts of the extracellular compartment is not the same and that there is a rapid preferential uptake of relaxants by the neuromuscular junction. This was demonstrated with radioactive d-chondrocurarine,[274] curarine,[395] and decamethonium.[394] Besides a special affinity, the fast selective uptake of relaxants by the end plate is probably due to its excellent blood supply. There is a close spatial relationship between capillaries and the end plate.[235]

Following the initial rapid fall in the concentration of d-Tc, due to distribution in the extracellular compartment, the drug disappears from the extracellular fluid with a half time of about 45 minutes.[235] It is probable that some d-Tc re-enters the plasma and is excreted in the urine,[235] while some may enter other sites (perhaps cellular) where it is destroyed or from which it is later slowly released.

C. Metabolism. With regard to their metabolic transformation in the body, the quaternary ammonium-type neuromuscular blocking agents may be divided into three groups. Members of the first group are metabolized almost completely, those of the second group, partially, and those of the third group are excreted unchanged, primarily by the kidneys. SCh, SECh, and other hydrolyzable, ester-type agents belong to the first group. SCh,[379,380] SECh,[146] murexine, and dihydromurexine[112,136] are hydrolyzed relatively rapidly by human plasma cholinesterase to their acid and alcohol components. SCh is hydrolyzed in two steps: first, it is broken down to succinylmonocholine and choline and then the succinylmonocholine is hydrolyzed to succinic acid and choline. In vitro, with a substrate concentration of 2.2×10^{-2}M, SCh is hydrolyzed at the rate of about 0.1 μM per 1 ml. of plasma per minute.[146,379,380] Because of the considerably lower substrate concentrations attained in the plasma after clinically used doses (about 3×10^{-5}M) and its rapid diffusion from the plasma to other parts of the extracellular compartment, the in vivo hydrolysis rate of SCh is considerably slower. Because of its low plasma concentration, alkaline hydrolysis probably contributes little to the in vivo breakdown of SCh. The enzymatic hydrolysis rate of succinylmonocholine by human plasma cholinesterase is 6 to 8 times slower than that of SCh.[132] As well as by plasma cholinesterase, succinylmonocholine is also hydrolyzed by an enzyme present in the liver, which seems to be specific for this compound.[168] SECh is hydrolyzed about 50 per cent faster by human plasma than is SCh.[146] Murexine and dihydromurexine are hydrolyzed by plasma cholinesterase at the rates of 0.3 and 5.0 μM per milliliter of plasma per minute, respectively.[136]

There is good correlation between the plasma cholinesterase activity and the duration of apnea caused by identical milligram per kilogram doses of SCh.[114,181,206,238] In female plasma, the hydrolysis rate of SCh is about 30 per cent slower than in male.[349,350] Plasma cholinesterase level is usually lower in liver disease[146,387] and in cachexia or malnutrition[105] and the duration of action of SCh is proportionally increased in these patients.[146,206] The simultaneous intravenous administration of procaine[142] or lidocaine[68] will inhibit plasma cholinesterase activity and potentiate and prolong the action of SCh. Marked potentiation and prolongation can be achieved by the use of hexafluorenium, a potent, selective inhibitor of plasma cholinesterase.[137,144,145]

Under normal circumstances, the average quantity of intravenously administered SCh

excreted unchanged in the urine is less than 3 per cent.[130] Following the administration of paralyzing doses of succinylmonocholine,[132,143] less than 15 per cent is excreted unchanged in the urine.[130]

In subjects with atypical forms of plasma cholinesterase[237,239] the enzymatic breakdown of SCh may be decreased out of proportion to that of ACh,[135,236] and its administration may result in unusually prolonged neuromuscular block.

d-Tc and dim-Tc are the two most important members of the second group. In man, about two-thirds of the injected d-Tc is destroyed in the body and one-third can be recovered unchanged in the urine.[233, 269,274] About one-half of intravenously injected dim-Tc is excreted unchanged in man.[274] It is probable that the site of the metabolic transformation of d-Tc[274,312,386] and also that of dim-Tc[274] is the liver. According to Marsh,[274] d-Tc is detoxified by means of catechol formation and oxidation to quinoid structures and dim-Tc undergoes demethylation.

Members of the third group include gallamine, benzoquinonium, decamethonium, and probably also other relaxants. These can be recovered almost quantitatively from the urine.[124,290]

VI. Altered sensitivity to neuromuscular blocking agents

Altered sensitivity to neuromuscular blocking agents may manifest itself in either an increased or a decreased reaction to normal doses. On occasion, the neuromuscular block may be irreversible.[221]

A. Decreased sensitivity. Decreased sensitivity to relaxant drugs is encountered less frequently than increased sensitivity. It can occur with both depolarizing and nondepolarizing agents in apparently normal subjects and also in association with various pathologic conditions. Thus, resistance to the neuromuscular effects of SCh, [146,257] decamethonium,[297] and benzoquinonium[188] was encountered in human subjects with no demonstrable pathologic conditions. Under pathologic circumstances, resistance to C10[62,64,346] and SCh[159] was observed in myasthenic subjects and to d-Tc[99] and laudexium,[100] in the presence of liver disease and natural or acquired tolerance to barbiturates and opiates.[165]

B. Increased sensitivity. Increased sensitivity to both depolarizing and nondepolarizing relaxants is encountered more frequently than decreased sensitivity. The clinical consequences of increased sensitivity may be serious. Its extreme manifestation, "irreversible curarization" is discussed in the next section. Besides the increased sensitivity caused by various well-defined pathologic changes, drugs, and other variables, it can also be encountered in subjects with no demonstrable pathologic or other causes. Increased sensitivity to customary doses of SCh in apparently healthy subjects, with normal plasma cholinesterase levels, was reported by several investigators.[9,34,115,282,366,402] It was also observed after 5 mg. test doses of d-Tc in nonmyasthenic subjects.[185] Pelikan, Tether, and Unna[307] state that 3 to 4 per cent of normal individuals may be as sensitive to d-Tc as myasthenic subjects. Prolonged apnea indicating hypersensitivity was reported after clinical doses of d-Tc,[91] gallamine,[73,98] or benzoquinonium.[98]

The hypersensitivity caused by pathologic changes and other variables has been discussed in other sections of this review. It should be emphasized, however, that, under clinical circumstances, increased sensitivity to both depolarizing and nondepolarizing neuromuscular blocking agents is encountered most frequently in debilitated patients with disturbance of fluid and electrolyte balance.

C. Irreversible curarization. Deaths associated with the administration of relaxant drugs may be caused by a variety of factors unrelated to their use. These were recently discussed by Paton[302] and Gray and his collaborators.[167] The irreversible apnea occasionally encountered after the use of SCh has been discussed elsewhere[147] and reviewed in other sections of this paper. The ensuing discussion will be lim-

ited to the irreversible curarization caused by nondepolarizing neuromuscular blocking agents.

Attention to cases of "neostigmine-resistance" was stimulated by Hunter[221] who reported on 6 such cases that came to his attention. Many more cases were reported in the voluminous correspondence, primarily in the *British Medical Journal*, elicited by Hunter's publication. Foster,[154] Burchell,[49] Burchell and Lamont,[50] and Gray, Dundee, and Riding[167] reported similar groups of cases.

The patients in whom irreversible neuromuscular block occurred were elderly, debilitated, or both. Most were operated on for the relief of intestinal obstruction and had clinical evidence of severe fluid and electrolyte imbalance. They did not seem to be unduly sensitive to the initial dose of d-Tc or gallamine used, and in some cases spontaneous respiration, although depressed, was present during [49,221] or after[49] operation. Although some of the patients described by Hunter[221] reacted temporarily to edrophonium, the neuromuscular block could not be antagonized by conventional or excessive doses of neostigmine.[49,154] Despite the maintenance of adequate respiratory exchange by intermittent positive pressure controlled respiration, the patient died of secondary circulatory failure[49,221] several hours after operation.

Potassium deficiency,[154,221] disturbance of the sodium-potassium balance,[167] adrenocortical insufficiency,[214] and other factors[49] were suggested as the cause of the irreversible block. Since the prolonged postoperative apnea encountered under the described circumstances is frequently resistant to corrective measures, it has been suggested that the use of nondepolarizing relaxants should be avoided in these patients.[221] Prolonged or irreversible postoperative apnea is said to be unlikely when neuromuscular blocking agents are administered cautiously in doses that will just give adequate surgical relaxation without paralysis of the activity of all the respiratory muscles.[124,131,214]

VII. Antagonists of nuromuscular blocking agents

The neuromuscular activity of both nondepolarizing and depolarizing relaxants can be antagonized by a variety of compounds. Antagonists of nondepolarizing relaxants will on occasion antagonize the second phase block[227] caused by depolarizing relaxants. There are compounds which antagonize the true or first phase depolarization block but they have no practical significance.

A. Antagonists of nondepolarizing relaxants. The antagonists of nondepolarizing relaxants include neostigmine bromide, edrophonium chloride, pyridostigmine bromide (Mestinon), Ro1-5733 [(2-hydroxybenzyl) trimethylammonium (bromide) dimethyl carbamate] and tetraethylammonium bromide.

1. Mode of action. It is generally believed that the effect of the antagonists of nondepolarizing relaxants is primarily due to their anticholinesterase activity, which results in the accumulation of ACh at, and the displacement of the relaxants from, the end plate.[196,242,293,351] Cohen[70] observed that the intravenous administration of edrophonium or neostigmine decreased the plasma level of d-Tc. The decrease paralleled the improvement in vital capacity and was temporary after edrophonium and permanent after neostigmine. This assumption

Table VII. *Relationship between anticholinesterase activity, anticurare effect, and therapeutic efficacy in myasthenia gravis of the antagonists of nondepolarizing relaxants*

Compound	*I_{50} value for red cell cholinesterase*	*Intravenous anticurare dose (mg./Kg.)*	*Relative efficacy in myasthenia gravis*
Neostigmine	2.3×10^{-7}	0.02	1.00
Ro1-5733*	1.0×10^{-7}	0.01	1.50
Pyridostigmine	4.5×10^{-7}	0.07	0.25
Edrophonium	1.1×10^{-5}	0.30	——

*(2-Hydroxybenzyl) trimethylammonium (bromide) dimethylcarbamate.

is corroborated by the finding that there is a close parallelism between the in vitro inhibitory effect of these compounds on human true (red cell) cholinesterase and their anticurare activity[133,134] or therapeutic efficacy in myasthenia gravis[126] (Table VII). Others, however, are of the opinion that neostigmine[329,330] and edrophonium[212,396] also have a direct depolarizing action at the neuromuscular junction. Randall[323] entertained the possibility that the free phenolic group of edrophonium might be, in part, responsible for the anticurare activity.

The antagonists are not equally effective against all nondepolarizing relaxants. They counteract the neuromuscular effects of d-Tc, dim-Tc, and gallamine more reliably than those of benzoquinonium[219] or laudexium.[100]

Because of their anticholinesterase and direct depolarizing effect at the end plate, the antagonists of nondepolarizing relaxants may intensify and prolong the true (phase I) nondepolarization block.[61a,301,374] This property of neostigmine and edrophonium was utilized to determine the type of block produced by quaternary ammonium compounds.[150,328] In contrast to this, the second phase block induced by C10[336,344] or SCh[9,74,147,161,182,198,199,336] may be reversed by neostigmine or edrophonium.[61a,147,199] Similar observations were made with hexamethylene-bis-carbaminoylcholine bromide (Imbretil).[91a,150,280,295]

2. Dosage, onset and duration of action. The dose and time relationships of the antagonists of nondepolarizing relaxants were investigated in both unanesthetized and anesthetized subjects. In unanesthetized man, 0.75 mg. neostigmine[265,266] or 10 mg. of edrophonium[265] antagonized the effects of doses of d-Tc which produced a 95 per cent decrease in grip strength. Doughty and Wylie[90] found that, in unanesthetized subjects who received 40 to 50 mg. of gallamine, 15 to 20 mg. of edrophonium caused only transient antagonism of the neuromuscular block.

In anesthetized subjects, neostigmine and edrophonium were used most frequently to antagonize the neuromuscular effects of nondepolarizing relaxants. Pyridostigmine, Ro1-5733, and tetraethylammonium were used by only a few workers.

a. NEOSTIGMINE. There is considerable variation in the recommended initial dose of neostigmine. Foldes[124] suggests that the initial dose should be between 0.5 and 1.5 mg. Doses of 1.25 to 2.5 mg. were used by Doughty and Wylie[90] and of 2.5 to 5.0 mg. by Gray.[162] It is generally accepted that the administration of neostigmine should be preceded by the intravenous administration of 0.65 to 1.3 mg. atropine[90,162,220] to minimize the possibility of muscarinic side effects. The full effect of a given dose of neostigmine develops in 2 to 4 minutes and lasts 30 to 45 minutes. Because of its relatively long duration of action, recurarization after its use occurs only infrequently.[100,139]

b. EDROPHONIUM. The recommended dose of edrophonium varies from 5 to 20 mg.[13,90,124,218,272] The onset of action of edrophonium is rapid and usually reaches its maxim within 45 to 90 seconds. Its duration, however, is brief and its effect is usually over, even after a 20 mg. dose, within 5 minutes. If during this time most of the relaxant displaced from the receptors is removed by the circulation from the end plate, the reversal of the neuromuscular block may be permanent.[13] Under clinical conditions, however, when, after prolonged administration of relaxants, the inactive sites of the intracellular compartment become saturated, the relaxant displaced by edrophonium may be readsorbed to the cholinergic receptors and as a result recurarization occurs frequently. Under such circumstances, an antogonist of longer duration of action should be used. Although the muscarinic side effects of edrophonium are less marked than those of neostigmine, Hunter[218] recommends that 0.65 mg. atropine should be used in conjunction with it.

c. PYRIDOSTIGMINE. The recommended dose of pyridostigmine is 5 to 10 mg.[41,328] Its action is slower in onset (about 4 minutes) and somewhat longer in duration than

that of neostigmine. Its muscarinic side effects are less marked than those of neostigmine, but its anticurare effect is also less reliable.[41] It should be administered together with 0.65 mg. atrophine.

d. Rol-5733. The inhibitory effect on red cell cholinesterase and anticurare activity of this neostigmine analog is about twice as great as that of neostigmine.[134,249] Its recommended initial dose is 0.01 mg. per kilogram. When administered after gallamine, it causes no fall in pulse rate or blood pressure. Swerdlow and associates[367] observed, however, in unanesthetized subjects that its muscarinic effects are only slightly less than those of neostigmine and recommend that it also should be used together with atropine.

e. TETRAETHYLAMMONIUM. In 1.5 to 2.0 mg. per kilogram doses tetraethylammonium was used by Stovner[365] to antagonize the neuromuscular effects of d-Tc. Its use is associated with some fall in blood pressure. At the present time, it does not seem to offer any advantages over other antagonists in clinical use.

3. Side effects and complications. Besides their neuromuscular activity, the antagonists of the nondepolarizing relaxants may also have muscarinic effects of various severity. These were recently described in a comprehensive paper by Rollason.[332] The muscarinic side effects are most pronounced after neostigmine and are least disturbing after edrophonium. They may be manifested by increased salivation and bronchial secretions, increased intestinal motility, abdominal cramps, slowing of the pulse rate, shift of the cardiac pacemaker, and, in extreme cases, cardiac arrest. In asthmatic patients, severe bronchospasm may be precipitated by neostigmine and other anticholinesterases.

In conscious subjects, the intravenous injection of 1.25 mg. of neostigmine caused severe and prolonged muscarinic effects.[90] The intensity and duration of the side effects were decreased by the previous administration of 1.3 mg. atropine. Only slight muscarinic effects of brief duration were observed after the intravenous administration of as much as 20 mg. of edrophonium.

In anesthetized subjects atropine administered before or together with neostigmine may decrease the intensity, but by no means will completely eliminate the muscarinic effects. There has been considerable divergence of opinion regarding the protective effect of atropine against the cardiac effects of anticholinesterases. Some observers believe that, initially, atropine, instead of tachycardia, may cause bradycardia[16,333] and potentiate the vagotonic effect of neostigmine. Others are of the opinion that atropine, by blocking the vagus, may cause changes in cardiac irritability similar to that seen after the use of adrenergic drugs.[225,316] This is more likely to occur in patients anesthetized with cyclopropane,[225] but can also occur with other anesthetic agents, especially in the presence of carbon dioxide retention.[230,316]

Most observers agree, however, that the intravenous administration of 0.65 mg. atropine causes a moderate to marked rise in pulse rate in the majority of patients, no change in some, and a moderate decrease in only an occasional one.[220,332,363,403] When neostigmine is injected together with or after atropine, the bradycardia is usually preceded by an initial tachycardia.[220] The intravenous injection of 5 mg. of pyridostigmine caused a 6 to 60 per minute decrease in pulse rate.[332] When 5 to 10 mg. of pyridostigmine is administered together with 0.65 mg. atropine, there is a consistent increase in pulse rate.[41]

Under cyclopropane anesthesia, electrocardiographic changes followed the intravenous administration of 0.5 to 2.0 mg. neostigmine.[225] The incidence and severity of atrioventricular block, depression of the sinus node, or arrest of the sinus rhythm were proportional to the dose of neostigmine. The intravenous administration of 0.8 mg. atropine at the height of the neostigmine effect caused bursts of ventricular tachycardia and, in one case, ventricular flutter. Less marked electrocardiographic changes after neostigmine were also noted

by Rollason[332] under other forms of anesthesia.

Neostigmine alone[391] or in conjunction with atropine[69,106,195,267] caused sudden death from cardiac arrest in several patients. Two other patients were resuscitated after neostigmine-induced cardiac arrest.[30, 254] Death after neostigmine is more likely to occur in vagotonic patients with sinus bradycardia, asthma, peptic ulcer, or jaundice, or in those whose vagus tone is increased by digitalis, cyclopropane, or halothane.[332] The autonomic effects of the relaxants used should also be considered. The muscarinic effects of neostigmine may be more marked after benzoquinonium[219] and the vagolytic effect of atropine after gallamine.

In addition to their cardiovascular effects, the antagonists of neuromuscular blocking agents may cause death by at least two other mechanisms. The first one is neuromuscular block caused by excessive doses of neostigmine[61a] and the second is recurarization after the use of antagonists in inadequately supervised subjects.

It has been demonstrated in animal experiments[42] that large doses of anticholinesterases may produce neuromuscular block. Such a cholinergic block is not uncommon in myasthenic subjects who take an overdose of anticholinesterase ("cholinergic crisis"),[299] and its possibility in anesthetized subjects was also suggested,[124,154, 222,348] and recently conclusively demonstrated by Churchill-Davidson and Christie.[61a] It is conceivable that in some cases of "neostigmine-resistant curarization," the large doses, as much as 15 mg. within 60 minutes,[154] of neostigmine caused the irreversible block.

Recurarization may occur in patients in whom the neuromuscular effects of nondepolarizing relaxants were antagonized by anticholinesterases.[100,131,139] The probability of this complication after the use of edrophonium is well recognized. In general, however, less attention is paid to the possibility that the longer-acting anticholinesterases may be redistributed from the end plate before the neuromuscular blocking agents displaced by them are excreted or detoxified. Another factor which may cause recurarization is rapid deterioration of muscle strength due to exercise after seemingly complete recovery from the effects of nondepolarizing relaxants.[135] Such exhaustion of the respiratory muscles in the inadequately supervised patient may lead to serious consequences.

B. Antagonists of depolarizing relaxants. The antagonists of depolarizing relaxants may be divided into two groups. The first consists of pentamethonium and hexamethonium which antagonize the neuromuscular effects of C10 in cats.[303,305] Organe and coworkers[298] found that 30 mg. pentamethonium given at the height of the C10 paralysis accelerated recovery. Other observers reported that the antagonistic effect of pentamethonium[173,194,266] and hexamethonium[216,217] on intravenous administration is not reliable and their use may be followed by severe hypotension.[173,193,217] The intra-arterial injection of 5 mg. pentamethonium, however, consistently antagonized the C10-induced neuromuscular block.[173,189]

The second group consists of B.W. 49-204, a 2-stilbazoline derivative, and B.W. 51-212, a benzhydril piperazinium derivative. The former antagonizes C10[310] and the latter[109] both C10 and SCh in dogs and cats. Their antagonistic effect in man, however, is unreliable.[58,116,385]

C. Miscellaneous compounds with antagonistic effect. Several other compounds were also reported to antagonize the neuromuscular effects of depolarizing or nondepolarizing relaxants. Although they will be mentioned here, the experimental evidence of their efficacy is usually inconclusive. Galeotto and Rizzi[157] reported that pantothenic acid derivatives antagonize both depolarizing and nondepolarizing relaxants. Thiamine was found to have antagonistic effect on the neuromuscular effects of hexamethylene bis-carbaminoylcholine.[295] According to Jiri,[228] ACTH may also antagonize the unusually prolonged effects of relaxant drugs.

VIII. Clinical implications

Consideration of the pharmacologic effects of neuromuscular blocking agents and the influence of physiologic states, pathologic conditions, other drugs and variables on these effects is the best guide for their safe and efficient application in clinical medicine. The problems to be faced by the anesthesiologist when using relaxants include: (1) the choice of agent; (2) the dosage and mode of administration of the relaxant of choice; (3) the advisability of the use of more than one agent in the same patient; (4) the advisability and the technique of the use of antagonists; (5) the diagnosis and treatment of untoward reactions.

A. The choice of neuromuscular blocking agents. The choice of neuromuscular blocking agents depends on several factors, including: (1) the desired duration of action; (2) the choice of general anesthetic agent; (3) the presence of complicating pathologic conditions; and (4) the site of the operative intervention.

1. Duration of action. When very short duration of action is required, the agents of choice are SCh or SECh. These drugs, when used in moderate doses, have a rapid onset and a duration of action of 2 to 5 minutes. Because of this they are eminently suitable for the production of muscular relaxation for performance of endotracheal intubation, endoscopies, reduction of fractures, abdominal-pelvic examinations, dental extractions, etc. Their use has been questioned in ambulatory patients because of the high incidence and severity of muscle pain reported after their administration.[60] The development of pronounced muscular twitching, which is probably associated with the severity of postanesthetic muscle pain, can be minimized by the slow intravenous injection of moderate doses,[124] and perhaps even more by the administration of small, in themselves ineffective doses of d-Tc (5 mg.) or gallamine (20 to 30 mg.).[60,386]

When muscular relaxation of longer duration is required, long-acting, nondepolarizing agents, in repeated fractional doses, or SCh in continuous infusion should be used.[124] SCh can also be used in small fractional doses if plasma cholinesterase is selectively inhibited by hexafluorenium.[137]

2. Choice of anesthetic agent. Theoretically in the correct dose range, any muscle relaxant may be used with any general anesthetic agent. From the practical point of view, however, certain combinations are preferable to others. Thus, for example, since ether potentiates d-Tc[78] or gallamine,[124] and has no effect on[139] or antagonizes the neuromuscular effects of depolarizing drugs,[374,404] nondepolarizing agents should preferably be used with it. The administration of the combination of small doses of d-Tc (3 to 6 mg.) or gallamine (20 to 60 mg.), in conjunction with ether, results in adequate, easily controllable relaxation.[244a] Since both ether and gallamine tend to produce tachycardia, the relaxant of choice with ether is d-Tc.

The combined effects of certain relaxants and anesthetic agents on the autonomic innervation of the circulatory and respiratory systems speak for or against the use of such combinations. For example, benzoquinonium, which tends to produce bradycardia,[11] should not be used with cyclopropane or halothane which also tend to slow the heart rate. d-Tc seems to potentiate the hypotensive effect of halothane,[44,230] and therefore, these two agents should not be used together. In contrast, since gallamine has a tendency to counteract the halothane-induced bradycardia and hypotension, the combination of these two agents seems advantageous.[402a]

3. Underlying pathologic states. In myasthenia gravis and some forms of carcinomatous neuropathy all muscles are sensitive to nondepolarizing drugs.[21,95] In contrast, the sensitivity of the various muscles toward depolarizing agents can vary in these patients.[61] Involved muscles may be hypersensitive,[24] while noninvolved muscles may show normal or decreased sensitivity.[61] Because of this, it seems safer to use very small doses of nondepolarizing relaxants than depolarizing drugs for the

production of surgical relaxation in these patients.[124] The administration of nondepolarizing agents in doses sufficient to produce adequate surgical relaxation of noninvolved muscles, may cause prolonged and profound depression of involved muscles.[24]

In patients suffering from asthma or other allergic conditions, the use of d-Tc, laudexium, or Prestonal, because of their more pronounced histamine-liberating properties,[32,72,180,328] and benzoquinonium, because of its vagus stimulating effects,[11,120] should be avoided. Because of its depressant action on the vagus,[12,140] gallamine is the agent of choice in these cases.

Debilitated or dehydrated patients, especially if the dehydration is associated with disturbance of the electrolyte balance, are equally sensitive to depolarizing and nondepolarizing relaxants. It is advisable to decrease the dose of neuromuscular blocking agents in these patients and to try to achieve muscular relaxation without total paralysis of all respiratory muscles. Prolonged postoperative apnea and irreversible neuromuscular block are most likely to develop in such patients.

Despite the report that patients suffering from liver disease may show an increased resistance to nondepolarizing relaxants,[99] in clinical practice these patients may show an increased, instead of a decreased, sensitivity not only to SCh but also to other nonhydrolyzable depolarizing and nondepolarizing relaxants.[124] It is, therefore, imperative to administer not only SCh but also other relaxants in carefully graded doses. Despite the fact that plasma cholinesterase activity is usually decreased in these patients, no untoward effects will result from the administration of SCh provided that the dose has been adjusted to the decreased plasma cholinesterase level.[147]

In kidney disease, the neuromuscular blocking agents which are primarily excreted unchanged in the urine may have a prolonged effect. This usually occurs when these relaxants are used for prolonged periods and the inactive tissue depots of the extracellular compartment become saturated. No untoward effects should be expected when only a single moderate dose of a neuromuscular blocking agent is used. It is suggested that, in the presence of decreased kidney function, hydrolyzable agents should be selected for the maintenance of relaxation in prolonged surgical procedures. To avoid accumulation of succinylmonocholine with the prelonged administration of SCh, the use of small doses of SCh and hexafluorenium combined may be employed.[137]

Most available evidence indicates that, after their use in doses which produce adequate relaxation in the mother, neuromuscular blocking agents do not penetrate the placental barrier in high enough concentrations to produce neuromuscular block in the fetus.[75,79,204,246] The main considerations with regard to the use of muscle relaxants in obstetrical practice should be that the mother be adequately oxygenated throughout anesthesia, and that the ganglionic effect of the muscle relaxant should at no time produce significant fall in the maternal blood pressure and the fetal blood pressure dependent on it.

4. Site of operation. It is generally accepted that SCh causes a significant rise in intraocular pressure.[89,208,260] Consequently, its use in ophthalmic surgery is contraindicated in patients in whom even a transient rise of intraocular pressure should be avoided. It has been reported that SCh may also cause bradycardia[47,259,275,338] and transient circulatory collapse[275] after relatively large single doses. This is most likely to occur in infants, young children, and patients undergoing pelvic surgery. In the latter it was assumed to be due to stimulation of the pelvic division of the parasympathetic system.[339] The frequency of this phenomenon, however, is not great enough to influence the choice of a relaxant in gynecologic surgery.

B. Dosage and mode of administration. As the name implies, muscle relaxants should be used for the production of muscular relaxation, and not to cover up inadequate general anesthesia. They should be

employed in the smallest dose which will provide the necessary relaxation for the performance of the contemplated surgical procedure. With very few exceptions, they have no place in the management of surgical procedures which do not require muscular relaxation.

Because of the considerable individual variation in sensitivity to the neuromuscular effects of relaxants, the use of a small test dose is advisable in many, and imperative in patients in whom there is reason to believe that increased sensitivity to neuromuscular blocking agents might be present.[27,165] As previously discussed, patients in poor physical condition caused by fluid and electrolyte disturbances, anemia, hypoproteinemia due to liver or kidney disease or malnutrition,[372] chronic infections, or malignancy may be equally sensitive to depolarizing and nondepolarizing agents. Patients with low plasma cholinesterase activity, due to chronic subclinical organophosphorus intoxication[17a,272a] or quantitative[114] or qualitative[151,238,240] changes in this enzyme, may show extreme sensitivity to hydrolyzable neuromuscular blocking agents. Unfortunately the presence of these conditions in the majority of cases cannot be suspected either from the history or from the physical examination. Admittedly, in a busy operating room routine, it is often hard to find the extra five minutes necessary for the administration and the observation of the effects of a test dose. On the other hand, the time involved in testing the effects of relaxant drugs becomes negligible when compared with the many hours that might be spent, on occasion fruitlessly, in trying to resuscitate patients who reacted abnormally to normal doses of relaxant drugs.

In selecting the initial dose of relaxants the various factors that may alter their effects should be carefully considered. The recommended initial doses of the neuromuscular blocking agents have been listed elsewhere.[124] The selected initial dose should be injected intravenously in about 30 seconds. When a depolarizing relaxant like SCh is used, it is advisable to inject one-fourth of the initial dose very slowly and then follow with the rest at a somewhat more rapid rate. With this method of administration, muscular fasciculations and twitching can be minimized and the incidence and severity of postoperative muscle pain can be diminished. This is especially important if these drugs are administered to outpatients or to others who will be ambulatory within relatively short periods after the termination of anesthesia.

The best guide for the determination of the size of fractional doses is the observation of the effect of the initial dose. If the initial dose has a somewhat longer effect than expected, then the size of the fractional dose should be about one-fourth of the initial dose. In patients in whom the effects of the initial dose wear off more rapidly, the first fractional dose may be half of the initial dose. Fractional doses, in general, should be administered when relaxation of the surgical field starts to become inadequate or when increasing respiratory tidal volume suggests that their effect is gradually wearing off. With increasing length of anesthesia, the size of fractional doses can usually be diminished and the interval between their administration increased. The last fractional dose, the size of which should be adjusted to the time of the administration of the preceding dose, should be given just before closure of the peritoneum.

If muscular relaxation is maintained with a continuous intravenous infusion of SCh, the drip rate should be so adjusted that it should produce adequate relaxation of the surgical field. In most instances, this can be achieved without completely abolishing the spontaneous respiratory activity of the patient. Should this be impossible or undesirable for some reason, the infusion should be temporarily discontinued at frequent intervals to ascertain that the patient is receiving a "just paralyzing" dose of SCh.

Laryngeal spasm is perhaps the only legitimate indication of the rapid intravenous injection of an overdose of a muscle relax-

ant. If laryngeal spasm develops the most rapidly acting of the available muscle relaxants, preferably SCh, should be used in a dose (1.0 to 1.5 mg. per kilogram) that will ensure rapid and complete relaxation of the vocal cords. If laryngeal spasm develops in a patient in whom veins are not readily accessible, the intramuscular administration of a 4.0 to 6.0 mg. per kilogram dose of SCh will usually cause relaxation of the cords within two minutes. The intramuscular administration of neuromuscular blocking agents may also be resorted to in infants and young children or in adults in whom superficial veins are not readily available.

C. Combined use of relaxants. The combined use of different types of neuromuscular blocking agents seldom offers great advantages and, because of the increased hazards of complications and untoward reactions, this technique is not advisable under ordinary circumstances. A justifiable exception to this rule is the use of SCh for endotracheal intubation, followed by the administration of a nondepolarizing relaxant for the maintenance of relaxation during the rest of the anesthesia. Provided that the administration of the nondepolarizing relaxant is delayed until the effect of the dose of SCh wears off, this technique is unlikely to cause any complications. Another legitimate use of a nondepolarizing relaxant after a depolarizing drug is in treatment of tachyphylaxis to the depolarizing agent which develops in the course of anesthesia. Persisting in the administration of a depolarizing relaxant after the patient has become resistant to it might lead to prolonged postoperative apnea. Under these circumstances, the discontinuation of the depolarizing drug and continuation of the maintenance of muscular relaxation with small doses of a nondepolarizing agent is a logical procedure and is unlikely to cause any complications.[94] Here again, the nondepolarizing relaxant should not be administered before neuromuscular conduction is re-established after the discontinuation of the depolarizing drug.

Because of the marked inhibition by seemingly ineffective doses of nondepolarizing agents of the neuromuscular effect of subsequently administered depolarizing drugs,[266] excessive doses are necessary to produce relaxation with this sequence of administration.[94,149] Consequently, the maintenance of muscular relaxation with a depolarizing drug after the use of a nondepolarizing agent is pharmacologically unsound and clinically dangerous.[147]

D. Use of antagonists of muscle relaxants. With the correct selection and method of administration of muscle relaxants the use of antagonists should seldom be necessary. If the respiratory exchange or muscle tone at the termination of operation is inadequate, it is safer to oxygenate the patient by assisted or controlled respiration until satisfactory spontaneous respiration is established, than to use an antagonist. Should it become necessary to administer an antagonist, then this should be done with extreme care.

If apnea or inadequate respiratory exchange follows the use of a nondepolarizing relaxant, 10 to 20 mg. edrophonium should be administered intravenously. If edrophonium produces a temporary improvement of the respiratory exchange, then 0.4 to 0.6 mg. atropine followed in 2 to 3 minutes by 0.02 mg. per kilogram neostigmine may be administered over a period of 60 to 90 seconds. If this dose of neostigmine does not produce the desired effect within 3 to 4 minutes, more may be injected in 0.5 mg. increments about 5 minutes apart, until either the desired effect is obtained or no further improvement or deterioration follows the administration of the last dose. The pulse rate should be carefully observed before the administration of each fractional dose and, if bradycardia develops, additional small doses of atropine should be given. The administration of neostigmine in large single doses is not only dangerous,[332] but may actually cause neuromuscular block itself.[61a]

If the administration of edrophonium is ineffective, or if only partial recovery of

the respiratory activity can be achieved by neostigmine, then other measures, discussed below, should be applied.

Before edrophonium or neostigmine is employed to antagonize the depolarizing relaxants causing prolonged postoperative apnea, it must be determined whether the latter is caused by persistent neuromuscular block or by other factors. Only when all other possible causes have been eliminated should one resort to the use of anticholinesterases.[147]

Whenever antagonists of muscle relaxants have been employed to restore adequate spontaneous respiratory activity, the patient should be kept under close supervision for at least 30 to 60 minutes. This is necessary to avoid the possibly disastrous consequences of recurarization. As already discussed, recurarization after the use of an antagonist can occur by various mechanisms. These include shift of fluid from the extracellular to the intracellular compartment resulting in accumulation of the relaxant at the end plate; removal and excretion of the antagonist from the neuromuscular junction and readsorption of the relaxant to the cholinergic receptors; or exhaustion of the respiratory musculature by the effort necessary to maintain adequate spontaneous respiration in the presence of residual amounts of nondepolarizing relaxants at the end plate.[135]

E. Diagnosis and treatment of untoward reactions. The most serious complication that may accompany the use of muscle relaxants is prolonged postoperative apnea or respiratory depression. This complication is most frequently, but by no means always, due to the residual effect of neuromuscular blocking agents. Other causes of postoperative apnea[147,167,302] include: (1) reflex breath holding, elicited by the presence of the endotracheal tube; (2) central depression caused by the agents used for the maintenance of general anesthesia, or, in rare instances, the accumulation of carbon dioxide; (3) hypocarbia produced by excessive hyperventilation during anesthesia; (4) atypical response of the respiratory center to prolonged controlled respiration; (5) irreversible changes, either in the central nervous system or in the neuromuscular apparatus, in moribund patients. The diagnosis and treatment of prolonged postoperative apnea after the use of neuromuscular blocking agents have been discussed elsewhere,[147] but because of its great clinical significance will be again reviewed briefly.

Reflex breath holding may be diagnosed by stimulating the tracheobronchial tree with a suction catheter. This frequently evokes violent coughing in the apneic patient, indicating adequate power of the respiratory muscles. On occasion, deflation of the cuff of the endotracheal tube or the removal of the tube itself will reinstate spontaneous respiratory activity. Naturally, when the endotracheal tube is removed for diagnostic purposes, the anesthetist should be ready to reinsert it rapidly if the apnea is due to some cause other than breath holding. Central depression caused by narcotic analgesics used for supplementation of nitrous oxide–oxygen, thiopental sodium anesthesia can be reliably antagonized with 0.02 mg. per kilogram levallorphan. The effect of levallorphan is usually manifested in 3 to 5 minutes. On occasion, respiratory depression, caused by barbiturates, may be counteracted by the intravenous injection of central nervous system stimulants such as Metrazol, or Ritalin. If the central nervous system depression is due to an inhalation anesthetic agent, controlled respiration with a high flow of oxygen will facilitate its elimination and resumption of spontaneous respiratory activity. If hypocarbia is suspected to be the cause of the apnea, controlled respiration at a relatively slow rate (8 to 10 per minute) and a tidal volume of 400 to 600 ml. will usually result in the accumulation of enough carbon dioxide to trigger the respiratory center.

If there is reason to believe that the prolonged postoperative apnea is due to a residual neuromuscular block, the effect of edrophonium should be tested first, after

the use of either depolarizing or nondepolarizing relaxants. As already discussed, if after the administration of edrophonium there is temporary improvement, it should be followed by the cautious administration of atropine and neostigmine. If the administration of edrophonium is ineffective, the use of neostigmine is not recommended. Under these circumstances, an indwelling catheter should be inserted in the bladder and an attempt should be made to produce diuresis preferably by the use of an osmotic diuretic like 50 per cent dextrose or 30 per cent urea. After the development of diuresis the administration of edrophonium should be repeated and, if effective, should be followed by neostigmine. If diuresis itself, or combined with edrophonium, does not result in restitution of adequate spontaneous respiration, the cautious administration of potassium chloride may be tested. Sixty to eighty milliequivalents of potassium chloride dissolved in 1,000 ml. of 5 per cent dextrose may be infused intravenously at the rate of 80 to 100 drops per minute. It is advisable to observe the cardiac effects of the intravenous potassium administration by continuous electrocardiagraphic monitoring. If potassium alone is ineffective, edrophonium should again be tried after 200 to 300 c.c. of this solution has been infused intravenously.

In cases where neostigmine is only partially effective, the intravenous administration of 20 to 50 mg. of ephedrine may result in further improvement of respiratory activity.[51,410]

If all attempts to restore respiratory activity have failed, patients should be kept on controlled respiration, preferably with an intermittent positive-negative pressure mechanical respirator. Measures should be taken for the maintenance of adequate circulation. These should include, whenever indicated, digitalization. The reactivity of the end plate to edrophonium should be tested periodically. In the event of a positive reaction the administration of atropine and neostigmine will usually result in permanent restoration of spontaneous respiratory activity.

Addendum: Centrally acting relaxants

There are numerous compounds capable of producing muscular relaxation without affecting neuromuscular transmission. Their site of action is at various levels of the central nervous system. They all depress transmission of impulses primarily in the polysynaptic pathways and have little or no effect on monosynaptic pathways, motor nerves, or muscles. Besides their muscle-relaxant activity, they may also exhibit, to a variable extent, many other pharmacologic effects. Some of these, e.g., anticonvulsive action, potentiation of barbiturate anesthesia and local anesthesia, were present in mephenesin, the first of this group of compounds extensively investigated.[22] Other centrally acting relaxants may also have analgesic, antipyretic, sedative, tranquilizing, and autonomic effects. They may affect the reticular formation, influence arousal, and change the electroencephalographic pattern.

The pharmacologic properties of the centrally acting relaxants were adequately investigated in animal experiments but little controlled experimental work was carried out with them in human subjects. Consequently, in this review, only their clinical application will be considered briefly. Those interested in further details are referred to a symposium of the New York Academy of Sciences.[281]

A. Use in anesthesiology. Shortly after the description of its pharmacologic properties by Berger and Bradley,[22] mephenesin (Myanesin) was used by Mallinson[270] for the production of muscular relaxation during anesthesia in about 15 mg. per kilogram doses, injected intravenously in the form of a 10 per cent solution. He reported that mephenesin potentiated the hypnotic effect of barbiturates and that barbiturates markedly potentiated the relaxant effects of mephenesin so that good abdominal relaxation could be achieved with little or no respiratory depression, and he thought that

mephenesin had definite advantages over curare. Marston[273] was equally impressed with mephenesin. Its use in anesthesiology was investigated by several workers.[17,57,156,169,171,322] Their findings did not justify the early enthusiasm regarding its superiority over curare. Administered intravenously in doses of 30 mg. per kilogram to unanesthetized subjects,[171] it caused no appreciable loss of muscle power and had little effect on sensorium. Nystagmus and loss of convergence of the eyes were the only objective neurological signs encountered. Occasionally, slurring of speech was also noted. In some subjects, local irritation or thrombophlebitis developed at the site of injection. Many had hemoglobinuria and albuminuria. Marked hemoglobinuria was noted earlier by Pugh and Enderby,[322] and Hewer and Woolmer[193] reported a case of fatal kidney damage attributed to the use of mephenesin. Because of these complications, the use of mephenesin in anesthesiology was abandoned. No other centrally acting relaxant was used to any appreciable extent for the production of muscular relaxation during surgery. The use of mephenesin for the production of regional nerve blocks[118] and as an adjunct to postoperative pain relief after orthopedic surgery[347] was investigated but was not found suitable for clinical application.

Table VIII. *Centrally acting muscle relaxants*

Generic name	*Trade name*	*Oral dose (Gm.)*
Mephenesin	Myanesin Tolserol Lissephen	0.50 to 1.50
Meprobamate	Equanil Miltown	0.20 to 0.80
Carisoprodol	Soma	0.40 to 1.20
Zoxazolamine	Flexin	0.25 to 1.00
Styramate	Sinaxar	0.20 to 0.80
Chlorzoxazone	Paraflex	0.25 to 1.00
Methocarbamol	Robaxin	0.50 to 1.50
Chlormethazanone	Trancopal	0.10 to 0.20

B. Other uses. The centrally acting relaxants were used for the treatment of a variety of conditions including: (1) muscle spasms caused by trauma, rheumatoid conditions, and various neurological disorders; (2) rigidity, tremor, incoordination, and involuntary movements associates with pathologic changes of the central nervous system; (3) strychnine poisoning; (4) tetanus. Stephen and Chandy,[362] Hunter and Waterfall,[223] Schlesinger and associates,[343] Berger and Schwartz,[23] Gammon and Churchill,[158] and Smith[355] were among the first to use mephenesin in the treatment of various chronic conditions. Jacoby and Boyle[226] used it in the treatment of strychnine poisoning and Belfrage[19] and Davison and his co-workers[85] first employed it for the treatment of tetanus.

A critical review of the voluminous, and often conflicting, literature on the advantages and disadvantages of the numerous centrally acting relaxants now available for clinical use is beyond the scope of this review. Consequently, the discussion of the centrally acting relaxants will be limited to the dosage of the most widely used compounds (see Table VIII) and a few remarks on some of their pharmacologic effects of clinical significance.

Of the compounds listed, mephenesin, styramate, chlorzoxazone, methocarbamol, and carisoprodol have little tranquilizing or stimulating effect. Meprobamate and chlormethazanone, however, have marked tranquilizing, and zoxazolamine[356] some stimulating, effect. Therefore, when besides muscular relaxation stimulation is also required in depressed patients, the agent of choice is zoxazolamine. When tranquilizing or sedative effect is also desirable, in agitated states or in tetanus,[8] meprobamate or chlormethazanone is preferred.

Conclusions

The impact of the advent of neuromuscular blocking agents on our present un-

derstanding of the physiology of neuromuscular transmission, on the potentialities of anesthesia, and indirectly on the widening of the horizons of surgery has been great. It is unlikely that the anesthesiologist of the future will use the relaxant drugs presently employed. The muscle relaxants now at our disposal are far from free of unwanted effects. Untoward, occasionally fatal, reactions may accompany their use, often without warning, even though they are employed in accordance with the presently accepted concepts of their pharmacologic properties. Consequently, even should there be no further developments in our understanding of the physiology of neuromuscular transmission or the pharmacology of relaxant drugs, the search will continue for better agents. These new relaxants will probably be short-acting nondepolarizing compounds. Their pharmacologic effects and fate in the organism will be little affected by pathologic changes, general anesthetics, and other drugs. Their breakdown products will have no neuromuscular effect and in the rare instances when an atypical response makes it necessary they will be reversible by harmless antagonists. The eventual direction of the further development of neuromuscular blocking agents, made possible or necessitated by changing concepts of neuromuscular transmission and block, cannot at this time be predicted. It seems to be certain, however, that, barring unexpected developments in the field of general anesthetic agents, the relaxant drugs are here to stay.

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Symposium on the study of drugs in man

Part III. Human experimentation in medicine Moral aspects

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To avoid ambiguities, a theologian generally begins a consideration of this kind by defining as precisely as possible the terms of the discussion as he understands them, for it often happens that moralists and physicians use the same terminology in somewhat divergent senses. If these possible differences in meaning are not made initially apparent, the unfortunate result will be mutual misunderstanding.

To the theologian, medical experimentation usually connotes either the use of treatments which are not as yet fully established scientifically, or the use of procedures precisely for the purpose of discovering some truth or of verifying some hypothesis. The notion for us further presupposes that the subject is thereby exposed to some significant degree of risk or inconvenience; for if this latter element is lacking, there is little or no moral problem involved.[1]

By definition, therefore, experimentation admits of two possible purposes: benefit to the individual patient who submits to experimental treatment and/or the advance of medical science and consequent benefit to the common good of future patients in general. According as one or the other purpose is sought exclusively, or at least is paramount in the intention of the physician, two distinct moral problems present themselves. The first yields more easily to solution, both medically and morally. The second, which currently represents the more urgent problem in medical circles, is considerably more involved as a moral question.

Experimentation for the benefit of the patient

When the good of the individual patient is the physician's exclusive or predominant concern, the canons of good medicine will dictate the course of treatment which it is the doctor's moral obligation to provide. For the doctor is always first and foremost his patient's agent in the sense that he is contractually committed to the total best interests of that patient. Thus, for example, if there is a sure cure available in a given instance, it should ordinarily be employed in preference to treatment of doubtful efficacy; or if the only choice of remedy lies among several which are at best doubtful, the most promising of these should generally be used. In other words, the patient is en-

titled in justice to the surest means reasonably available for achieving the object of his medical contract, viz., the cure or control of his malady. Since this is the patient's right, the doctor's corresponding obligation is immediately clear.

It is also true, however, that if a proved remedy would entail exceptional expense, pain, or other inconvenience, the patient may be justified in choosing instead a procedure whose effectiveness is as yet incompletely established, but which circumvents the considerable disadvantage presumably inherent in his using the proved procedure. The patient, in other words, may legitimately run the risk, even though it be considerable, of a less certain remedy, provided that there is sufficiently serious reason for so doing. A fortiori, if there is little or no risk involved in accepting a remedy of dubious efficacy, no one would deny the patient's right to make such a choice for any reasonable motive. Actually this latter would not be experimentation in the strict sense of the word.

But it should be clear that any such decision or choice is the patient's prerogative and not the doctor's. Hence the doctor must prefer the certain to the uncertain remedy, the more probable to the less probable, unless the patient's legitimate choice to the contrary is explicitly expressed either by him or his juridical representative, or unless this consent to another procedure may be reasonably presumed. And since by supposition the patient in this instance represents the doctor's sole or primary concern, common sense alone would make the same requirement.

Experimentation for the benefit of others

In order to discern the limitations which must be placed on human experimentation undertaken for the benefit of others, one must appreciate two basic moral truths. These are not exclusively Roman Catholic convictions, even though they have more than once been enunciated in the authoritative teaching of the Roman Catholic Church. Rather they are fundamental philosophical principles which should be evident merely upon analysis of the nature of man in his various relationships to others. In combination they protect society and its members from each of two sociomoral extremes of thought, neither of which is compatible with our human status viewed in proper perspective.

The first of these principles is simply a denial of that extremist attitude which we have come to identify as totalitarianism and which would subject the individual completely to the community or state by subordinating all individual rights to the prior claims of the common good. Such a philosophy in its most blatant form found expression in the experimental excesses encouraged and practiced under Nazism and later repudiated by the free world in the formulation at the Nuremberg medical trials of a ten-point statement of limitations to be placed on medical experiments performed on human subjects.

To put the same principle positively: with regard to his life and bodily integrity, each individual possesses a God-given right of immunity from unprovoked attack by any other person. Such is the dignity of the human person that even civil authority must respect that immunity as long as the individual does not, by crime against society, become a serious threat to the common good. No individual subject, therefore, can legitimately be considered an expendable member of the body politic to be exploited for the common good. For this reason it follows, in the words of Pius XII, that:

> . . . the doctor can take no measure or try no course of action without the consent of the patient. The doctor has no other rights or power over the patient than those which the latter gives him, explicitly or implicitly and tacitly.[2]

The practical impact of this truth lies in the fact that, as laudable as may be the desire to contribute to the advance of medical science, doctors are nonetheless initially restricted in their human experimentation by this inalienable right of the patient to

forbid such use of his organic entity; or, as the very first rule of the Nuremberg Tribunal expresses it, "The voluntary consent of the human subject is absolutely essential." That this consent can sometimes be legitimately presumed does not detract in the slightest from a doctor's total dependence upon patient consent, in some genuine sense of that term, for the right to intervene in any way which affects the subject's bodily integrity.[3]

The second pertinent principle denies what might be called extreme individualism on our part, and imposes certain fundamental limitations on each one's right to dispose of his own life and bodily members. Because of the dignity of his human nature, as already explained, man enjoys a large measure of independence from his equals, fellow men. But because of his creaturehood, he must also admit himself to be essentially dependent upon his Creator. In context this dependence means that man is not complete and absolute master of his life and being. He is not proprietor of himself, but rather a steward entrusted with the care of "property" which strictly belongs to God. He may, therefore, administrate this trust only in compliance with the divine will as manifested to him in various ways.

The first practical corollary from this principle is the natural-law prohibition against suicide. To intend directly the termination of one's own life is the usurpation of a right which belongs exclusively to God; for our earthly existence is our trial for a future life, a trial whose duration can rightfully be decided only by the Creator. There are circumstances in which we are justified in risking our lives by actions which are necessary for the achievement of some momentous good; but in such cases death, if it should occur, is the unintended by-product of an act legitimately performed for another purpose and is not imputable as a moral evil. Even for the very laudable purpose of advancing medical science, no one would be justified in making his own death the intended means to that end.

A second consequence of the same principle relates to bodily damage short of death which for one reason or another one might inflict upon himself or allow another to inflict. We are responsible to God not only for life itself but also for our physical integrity, and only within certain limits may we legitimately mutilate our bodies or suppress their natural functions. Pius XI expressed this age-old truth in these words:

> . . . Christian doctrine establishes, and the light of human reason makes it most clear, that private individuals have no other power over the members of their bodies than that which pertains to their natural ends; and they are not free to destroy or mutilate their members, or in any other way to render themselves unfit for their natural functions, except when no other provision can be made for the good of the whole body.[4]

The same principle was repeated by Pius XII on many occasions in such language as this:

> . . . [the patient] is not absolute master of himself, of his body or of his soul. He cannot, therefore, freely dispose of himself as he pleases. Even the reason for which he acts is of itself neither sufficient nor determining. The patient is bound by the immanent teleology laid down by nature. He has the right of *use*, limited by natural finality, of the faculties and powers of his human nature. Because he is a user and not a proprietor, he does not have unlimited power to destroy or mutilate his body and its functions.[2]

Implicit in the statement that man does not have unlimited power to dispose of his bodily members and functions is the concession that he does possess a limited right of self-disposition. However, relatively easy as it is to delineate certain areas in which we may or may not claim that right, its maximum limits are still matter for speculation among theologians.

Certainly the "immanent teleology" of which Pius XII spoke includes above all an essential subordination of each corporal member to the organic totality which comprises the individual person. It therefore follows, for example, that if an individual bodily member because of malfunction becomes a serious threat to the life or well-

being of the total man, that part may be sacrificed, if necessary, for the good of the whole. It is in this "principle of totality" that we find both justification for most legitimate surgery of a destructive nature and grounds, too, for condemning patently unnecessary surgery. Again in the words of Pius XII:

> . . . by virtue of the principle of totality, by virtue of his right to use the services of his organism as a whole, the patient can allow individual parts to be destroyed or mutilated when and to the extent necessary for the good of his being as a whole. He may do so to ensure his being's existence and to avoid or, naturally, to repair serious and lasting damage which cannot otherwise be avoided or repaired.[2]

But in a context of investigative procedures undertaken exclusively for the benefit of others, the more pertinent question relates to the ordination, if any, of our bodies and their members to the good of our fellow men. (Note that the term used is "ordination" and not "subordination"; for to admit subordination would logically lead to corollaries of an inadmissible totalitarian character.) It would seem to be theologically beyond doubt that the principle of charity—i.e., love—toward one's fellow man does legitimatize a certain degree of bodily self-sacrifice for altruistic motives. For example, not only are blood transfusions, skin grafts, and the like, unanimously admitted by theologians to be permissible, but the donors in these instances have been singled out for explicit commendation in papal documents. Going a substantial step further on the strength of the same principle, a good many moralists of highest repute vigorously defend some forms of organic transplantation *inter vivos,* always with certain qualifications which good medicine would likewise stipulate. And finally, although one may never intend his own death as a means of saving another's life, it is sometimes permissible deliberately to perform an heroic act which will have two immediate results, viz., the preservation of another's life and the unintended, but in the circumstances inevitable, loss of one's own. In none of these instances does any bodily benefit accrue to the donor subject—in fact, quite the contrary is true, especially where the sacrifice of an organ or risk to life is concerned.

To the theologian, therefore, it is clear that the "immanent teleology" of our corporal being does admit of a certain ordination to the benefit of others. In terms of experimental medicine, it is also evident that as the genuine necessity of investigative procedures becomes increasingly more urgent, one is morally justified in submitting to considerably more than a modicum of risk to life or bodily integrity. But where draw the line beyond which one may not permissibly go in this regard? No mathematical answer, applicable to all cases indiscriminately, is possible. As does the physician in any good medical decision, the moralist must weigh the pros and cons of individual cases, chiefly in an attempt to judge whether there is reason sufficient to justify the necessary risk or harm entailed in the particular procedure contemplated.

In attempting to come to his decision as to the morality of an experimental procedure not designed to benefit the subject, the theologian would accordingly operate on such generic norms as these:

1. When bodily damage and/or risk to life are insignificant, there is no valid moral reason for forbidding the subject to submit to the procedure in question.

2. No one may legitimately consent to a procedure which entails certain death as a necessary means of achieving the experiment's purpose. (Although there is good reason to suggest that a criminal already justly condemned to death might licitly choose this form of execution, such a contingency represents the sole possible exception to an otherwise universal absolute.)

3. In the vast intermediate area where hazard to life or health may range from notable to very serious, the maximum limit of permissible risk is not as yet sharply defined. Many of the specific problems involved are relatively new and will require more thought and discussion before they

can be settled with total satisfaction. At the present time it seems safe to say that a subject may for the benefit of others authorize and submit to any experimental procedure which will not seriously and permanently impair his functional integrity or cause a grave risk to his life. Implicit in this concession is the supposition that the procedure has been adequately tested short of human experimentation; that it promises reasonable hope of achieving a good proportionate to the risk; that there is proportionate necessity here and now for employing human subjects; and that all reasonable care is taken to avoid even unintended harm to any who submit to the experiment.

Summary and Conclusion

No attempt has been made in the course of this discussion to assess the morality of individual concrete cases of human experimentation. So numerous and varied are its species that such a treatment would be prohibitively lengthy. Rather an attempt has been made to indicate the generic moral principles which should comprise the basis of such an assessment whenever one is made.

Of primary importance among these requirements is the informed consent of the subject. As a very general rule this consent should be explicit, especially if the subject is to be exposed to any appreciable risk or inconvenience for the benefit of others. Presumed consent remains a speculative possibility in some few instances; but in the majority of practical cases, this presumption would be either unjustified or at very least inadvisable.

But consent of itself does not suffice to justify all human experimentation, since there are limits, as yet not defined with total exactitude, beyond which man is not morally free to go in disposing of his life or bodily entity. The circumstances of individual cases must be considered in order to determine whether there exists sufficiently serious reason for inducing whatever degree of risk or harm may be entailed in the contemplated procedure.

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(To be continued.)

Book reviews

Atomic [illegible], third edition, edited by Behrens, Cha[illegible] F. Baltimore, 1959, The Williams and W[illegible]lkins Company, 705 pages. $15.

This collaborative text is concerned with the various aspects of atomic and nuclear physics and radiation biology which would be of interest to the physician and those in allied professions. The twenty-five contributors, most of whom are affiliated with the Department of the Navy or with governmental research institutions, have presented the subject on the basis of varying proportions of personal experience and observations, and analysis of the extensive and diverse literature in the field. There is emphasis on those aspects of atomic science which are of military significance; however, this does not detract from the value of the work as a whole for readers whose interests do not lie in this direction.

The sections on atomic and nuclear physics which are written by the editor are an especially lucid presentation of what might be obscure or difficult to those whose familiarity with mathematics and physics is limited. The author succeeds in developing such subtle concepts of physics as the Heisenberg uncertainty principle, nuclear mass defect, and binding energies of nuclei in such a way as to be quite comprehensible to the intelligent layman. The development of atomic theory, the structure of the Bohr Atom, the periodic system, and the concepts of elementary wave mechanics are developed historically; and the nature of nuclear forces and natural and artificial nuclear transformations are also discussed. Using these concepts, the rationale behind nuclear reactors and fusion and fission bombs is explained. The nature of the ionizing radiations themselves is described and the methods for measuring their intensity are considered in some detail.

The biologic effects of ionizing radiation, the pathologic anatomy, diagnosis, and therapy of radiation injury are discussed in several chapters which follow. This section is considerably weakened by the fact that the consideration of fundamental biology and biochemistry is inadequate. Furthermore, a thorough analysis of the long-term effects of radiation, covering such subjects as genetic effects and carcinogenesis, seems slighted in favor of a detailed discussion of the morbid anatomy and therapy of acute radiation injury. In this general section there is, however, a cogent discussion of the toxicity of internally deposited radioactive material.

A chapter dealing with "the atomic bomb in action" is concerned with the blast, thermal, and radiation effects of atomic weapons on material and inhabitants of a community and incorporates a discussion of the changes in perspective which have come about since the last edition of this book was published (1953) as a result of the development of the "hydrogen" bomb. The editor then discusses "permissible" dosage and risk, and radiation protection and monitoring, and, based on these considerations and the civil defense literature, points out certain prerequisites for survival in atomic disaster. Although this problem is not considered at length, the obvious discrepancy between the minimum needs in the event of disaster and our present state of preparedness is appalling.

Over one-third of the book is devoted to the diagnostic and therapeutic uses of radioisotopes and particle accelerators. While this section is not intended to provide sufficient material to be used as a manual in a radioisotope laboratory, it provides enough on techniques in current use to enable the practitioner to decide if any of these would be applicable to a particular case. The avenues of current research are indicated and form a basis for a realistic appraisal of the prospect for new diagnostic and therapeutic uses of atomic energy.

William Beaver, M.D.

Experiment Perilous, by Fox, Renée C. Glencoe, Ill., 1959, The Free Press. 262 pages.

This book is a treatise on the social determinants of human behavior under stress. In particular, it focuses on the problems and stresses of a group of physicians and patients in a metabolic research unit of an unidentified but thinly disguised New England hospital where research was being conducted on the then newly isolated and synthesized hormones of the adrenal cortex. This was at a time when the steroids opened promising new horizons for the medical treatment of and radical surgical approach to many hopelessly incurable or fatal diseases, a period in recent medical history when this particular research team made outstanding contributions to our present-day concepts of the therapeutic potentials and limitations of these hormones. The members of the Metabolic Group were then young clinical investigators who shared with their equally relatively young but seriously ill research patients many problems and difficulties inherent in their small world-apart. Dr. Fox is concerned with the socially patterned way with which each group met these difficulties.

The author's relation to the doctors and patients of this research unit was that of a participant observer working with a larger integrated group of medical and social scientists studying various aspects of the responses of the human organism to stress. In her discussion of the significance of her observations on "Ward F-Second," the setting for her book, Dr. Fox points out that the uncertainties, limitations, moral ambiguities, and untoward consequences which the physicians of the Metabolic Group experienced are not problems unique to the clinical investigator. Physicians in practice frequently come face to face with the same problems and stresses. Similarly, the anxieties and fears, isolation and regimentation, and submission to imposing procedures and medical authority are not singular experiences of the research ward patient for to some degree they are shared by all patients. The author presents convincing evidence that "to some extent, irrespective of differences in personality, in the statuses they occupy and in the substantive details of their problems, groups of men confronted with great uncertainty, limitation, danger, and death will tend to arrive at similar ways of adjusting to them."

This book is highly recommended to physicians and others interested in the

ethical, moral, and sociopsychological aspects of human pharmacology and clinical investigation. It contains an extensive and scholarly annotated bibliography which provides excellent source material for further reading. The inclusion of recorded conversations, correspondence, and clinical notes also provides for some interesting highlights of medical information and human interest.

R. W. Houde, M.D.

Handbook of Circulation, edited by Dittmer, D. S., and Grebe, R. M., Wright-Patterson Air Force Base, Wright Air Development Center, 1959. 393 pages.

Have you ever wondered what the "normal" heart rate is in the dachshund or guinea pig? Perhaps you are interested in the circulation of reptiles and amphibians? Or do you want to know how the amplitudes of electrocardiographic waves differ with age? All the above information and a great deal more can be obtained from **Handbook of Circulation.** Information is lucidly set out in tabular form. There are numerous references which can be put to good use when a project is undertaken.

Some sections deserve special mention. It appears unnecessary in a work as advanced as this to describe how the different leads of the electrocardiograph are obtained and how standardization is achieved (pages 137, 138, 139). Information on the duration of electrocardiographic waves and intervals, and on their amplitudes in different age groups, is invaluable to the clinician in interpreting a borderline tracing.

Many other sections may be found valuable for a résumé of a subject which has advanced rapidly within the last few years, for example, blood coagulation and anticoagulants. There is a long section on drugs and chemical substances affecting the circulation directly or indirectly. The chapter on the effects of radiation will be useful to all in these days of missiles and atomic reactors. The hemodynamic effects of various mechanical and pathologic processes will be found interesting to physiologist and clinician alike.

This is an indispensable reference book for anyone engaged in cardiovascular research in man or animals. At a pinch, **Handbook of Circulation** may even be recommended as bedtime reading for not-so-busy internists, as it is bound to keep the reader awake for a long time: imagine the fascination of reading about the ion ratio necessary to maintain the beat of the isolated heart in various insects! This may well lead one to wonder about the techniques involved in this delicate procedure, and to insomnia. To put up with any but the minimum of use, however, the binding will have to be reinforced. It is sincerely hoped that this will be done with subsequent publications of this nature.

Edel Berman, M.B., Ch.B.

American Drug Index, 1960, by Wilson, C. O., and Jones, T. E. Philadelphia, 1960, J. B. Lippincott Company. 712 pages.

By all odds, the **American Drug Index** is the most complete compact list of drugs published in this country. It contains not only proprietary names but also generic and official names and synonyms of drugs in use, many no longer in use or even available, and a lot of the common irrational mixtures to boot. It is well cross-indexed, is reasonably up to date, and contains remarkably few errors and inconsistencies for an Index of its form and comprehensiveness which attempts annually to keep up with the confusion in drug nomenclature. It is an amazing compendium.

While it makes no attempt (and correctly so) to discuss the use of drugs, it does identify their major uses.

I would never be without the latest issue. The question is whether the internist who deals with a relatively limited number of drugs needs it. He will have to decide for

himself on the basis of the questions asked him and the questions which arise in his own mind which he cannot answer with the references he already has.

Walter Modell

A Pharmacologic Approach to the Study of Mind, edited by Featherstone, R. M., and Simon, A. Springfield, Ill., 1959, Charles C Thomas, Publisher. 399 pages. $10.75.

This monograph contains the papers presented in January, 1959, in the course of a symposium at the University of California's San Francisco Medical Center. It becomes quite obvious that the editors largely succeeded in their attempt to arrange a truly multidimensional coverage of the "pharmacologic approach to the study of mind." The very title of this symposium provoked controversy with some speakers, as it will with some readers. Different degrees of revolt were leveled by some participants against usage of the term "mind" in the context of pharmacologic studies: it ranges from outright rejection of Cartesian dualism (F. H. Meyers) to a most illuminating semantic analysis with the history of neurophysiology as background (Chauncey D. Leake).

One may not always be satisfied with the sequence in which certain topics come up for discussion. For instance, it seems to me that J. Elkes' scholarly contribution would be more appropriately placed at the opening of the symposium, rather than between technical papers. I base my argument on the fact that J. Elkes' paper constitutes a searching and profound analysis of the cultural and scientific climate of Western Society as the matrix for development and growth of psychopharmacologic inquiry; thereby, this paper puts the totality of the psychopharmacologic enterprise (and consequently the present symposium) into its proper perspective. Furthermore, it is rewarding at the outset to be shown the signposts that may be expected eventually to overcome the compartmentalization into behavioral sciences, basic neurological sciences, and the introspective approach. The remarks of Elkes on the potential usefulness of information theory as a conceptual tool in this area are most challenging. Yet I believe that the calculus of information theory will not be adequate for the purpose, unless allowance will be made to accommodate the vectorial magnitude of "meaning."

A critical review by S. S. Kety, covering drug action on circulation and energy metabolism, opens the series of technical papers. Udenfriend's paper on "psychochemistry" deals mostly with phenylpyruvic oligophrenia. It is, I believe, realized by many people that "psychochemistry" is as bad a term as "psychopharmacology." It also tends to create the impression of a newly instituted science and makes one forget that the chemistry of the nervous system fascinated men like Thudichum long before "psychochemistry" was baptized. B. B. Brodie outlines elegantly a grand unifying conception by interpreting a great amount of experimental information in terms of W. R. Hess' dichotomy between ergo- and trophotropic system. The former is identified with the reticular activating system, to the latter is attributed the property of a "serotonergic" neuronal apparatus. Unfortunately, this, like Udenfriend's paper, lacks references to the relevant literature. In striking contrast to this simplifying classification stands J. O. Cole's critical outlook on the complexities involved in understanding, evaluating, and influencing psychopathologic processes.

The following section of the monograph is devoted to what is called "non-empiric approaches from the basic sciences"; it is introduced by a concise statement on the essence of the scientific method. In this, E. Kun follows wisely the thoughts of K. Popper, and refers the reader to the 1935 edition of *Logik der Forschung;* fortunately an enlarged and revised English edition of this standard work is now also available *(The Logic of Scientific Discovery,* 1959). I fail

to see the reason for the "non-empiric" in the title and I fully sympathize with the objection raised by K. F. Killam in a subsequent paper. "Non-empiric" seems to carry the connotation of a priori or axiomatic; yet what is meant is, I believe, "conceptual." The same objection applies to E. Robert's allusion to a distinction between "empiric" and "non-empiric" contributions in science: do not the act of measurement and the process of verbalization by necessity impose a conceptual (or, if you wish, "non-empiric") element on "empiric" knowledge? In any case, if—as I take it—"non-empiric" stands for "conceptual," then it must be stressed that the subsequent paper by E. Callaway III, H. F. Hunt, K. F. Killam, and E. A. Zeller, are masterly expositions, each one in its own domain, of conceptualization in basic sciences. At the same time, these papers summarize the "empirical" contributions of the authors in their respective fields.

The third part, devoted to research design and clinical evaluation, does not—with a few exceptions—go beyond statements of broad generalities. No doubt there are many pieces of good advice in this section: recommendation for controlling variables, statements on the non-drug factors of importance (L. J. Epstein), comments on the applicability of stochastic models (Chauncey D. Leake), etc. But one misses the actual implementation of these devices and some solid examples to show just how they really work in practice. Convincing data do, however, add meat to the interesting study of J. A. Starkweather on situational influences on drug effects. These papers are followed by a lively discussion, spiced with witty remarks of R. Gerard.

Under the heading of "tranquilizers," T. N. Burbridge supplies a sketchy and incomplete account of their pharmacologic properties. L. H. Margolis revives, I believe, unfortunately the term "neuroleptic" which was considered eradicated from the literature for some time. If I understand it correctly, tranquilizers are viewed as a subclass of neuroleptics, but the distinguishing criteria appear—to say the least—"relaxed." The significant aspect of this contribution consists in the well-documented emphasis on dosage regime as a critical factor in the treatment with phenothiazines. The problems associated with combined drug treatment and psychotherapy are competently discussed by N. W. Winkelman, Jr.

To round off the broad coverage, there are papers on hallucinogens, monoamine oxidase inhibitors, and psychic energizers. While the former two sections proceed along the pattern and standards of the preceding part of the book, there appears unmistakably a decline of scientific rigor in the last section. Interesting viewpoints about actions and structure activity relation of hallucinogens are presented by J. M. Dille, L. G. Abood, and G. Alles. J. M. Dille, in addition, outlines the scope of a field of inquiry which one may call "pharmacology of subjective experiences." Together with a discussion of the therapeutic potential of LSD-25 (S. Cohen) and a scholary evaluation of psychological studies with hallucinogens (A. R. Holliday), this section, organized as a panel by J. M. Dille, is the most homogeneous and evenly balanced sequence of papers on any one common topic in the entire monograph.

The experimental work on monoamine oxidase inhibitors is competently covered by A. Horita and D. Liebowitz.

Papers by N. S. Kline and H. V. Agin on therapy with psychic energizers excel in optimistic perspectives. It may energize the reader to learn from the latter author that one of the agents under investigation "in addition to its accepted antidepressant qualities, has restorative, recuperative, reparative and rehabilitative qualities . . . ." Fortunately, there are also more balanced opinions available: J. O. Cole, earlier in the monograph, expressed some reservation with regard to these agents and V. J. Kinross-Wright stresses the wide gaps of factual knowledge in this field. This is also borne out by the pharmacologic discussion of F. H. Meyers.

It will be obvious by now that this monograph contains an impressive array of views on the topic of psychopharmacology. The far-sighted planning that must have preceded the arrangement of the symposium's program, and accordingly the publication of the monograph, is admirable. It is particularly to the credit of the editors to have made allowances for an adequate examination of psychopharmacology as a cognitive enterprise, and of its role in society. With respect to the latter aspect, A. Huxley had some thoughtful words to add. In its final form, however, the monograph suffers, in my opinion, from lack of conciseness. There are redundancies that could possibly have been avoided had the editors made more use of their editorial privileges. It is also a shortcoming that the monograph does not have a subject index. There are several typographical errors in the text. These are particularly disturbing when it comes to names: Tunturi is consistently mispelled as Tinturi. In the table of contents, appears Chanucey instead of Chauncey. I think that the photographs of participants at the symposium could have been omitted. On the credit side, however, this monograph constitutes an impressive document of current endeavors in, and future potentials of, a field of inquiry which, with the aid of chemical agents, attempts to bring the domain of subjective experience into the realm of scientific knowledge.

Gerhard Werner

The Physiological Basis of Diuretic Therapy, By Pitts, R. F. Springfield, Ill., 1959. Charles C Thomas, Publisher. 332 pages.

In 300 pages Dr. Pitts presents an unusually clear, simple, and comprehensive discussion of the most recent concepts of renal function and the dynamics of drug action as they apply to edema and its relief. To be sure, the terse style sometimes tends to be didactic. It is precisely this, however, which gives the book its very special flavor. The book is not an attempt at an extensive but noncommital résumé of the vast literature, although the views of others are indicated when necessary. Nor is it a source book. It does present the author's views in a format which makes it perfectly clear what and how he thinks about a subject to which he has devoted many years—and Pitts' views on renal physiology and pharmacology are worth hearing.

The book is intended for students of medicine, but those who have already acquired degrees need not fear it for, unlike many books intended for students who do not have the M.D., it is not overwhelmingly technical. It is not a therapeutic guide either. Somewhat less than one half of the book is devoted to physiologic problems, the remainder to the pharmacologic actions of diuretics. Because of the size of the book, the older and less important diuretics suffer from compression of material, while considerable space is devoted to the currently more important agents, the mercurials, the carbonic anhydrase inhibitors, and the chlorothiazide congeners.

The discussions of renal physiology are especially outstanding. Here Pitts' talent for making a very complex and highly technical subject understandable and bringing it within the grasp of the intelligent and normally informed reader is well demonstrated. The chapter on "Mechanisms of Renal Filtration, Resorption, and Excretion of Ions and Water" is a gem; it has everything—quality, clarity, brilliance. The countercurrent concept is well presented. Nor is the discussion of the pharmacologic action of the diuretics less well presented.

I would take issue with the title. As a pharmacologist I must point out that more than one half of the book is really devoted to pharmacologic problems. Despite this, I recommend this book highly, not only to those who would understand how this enormously important, hydra-headed group of drugs produces its effects, but also to those who use the drugs and should therefore know what they are really doing. In addition, it provides a really excellent, if

slimmed down, review of renal physiology and, in view of the crystal-clear light it sheds on the role of the kidney as the defender of electrolyte and water homeostasis, it is a good book for those who view disturbances of this sort with interest and would like to have a short and simple presentation of the subject.

Walter Modell

Books received

Handley, C. A., and Moyer, J. H.: The Pharmacology and Clinical Use of Diuretics, Springfield, Ill., 1959, Charles C Thomas, Publisher. 194 pages, $6.00.

Lotspeich, W. D.: Metabolic Aspects of Renal Function, Springfield, Ill., 1959, Charles C Thomas, Publisher. 214 pages, $7.50.

Modell, W., Editor: Drugs of Choice 1960-1961, St. Louis, 1960, The C. V. Mosby Company. 958 pages, $13.50.

Ryan, R. E.: Headache: Diagnosis and Treatment, St. Louis, 1957, The C. V. Mosby Company, 421 pages.

Stephenson, H. E.: Cardiac Arrest and Resuscitation, St. Louis, 1958, The C. V. Mosby Company. 378 pages.

Welt, L. G.: Clinical Disorders of Hydration and Acid-Base Equilibrium, Boston, 1959, Little, Brown & Company. 336 pages.

Wilson, A., and Schild, H. O.: Clark's Applied Pharmacology, Boston, 1959, Little, Brown & Company. 750 pages.

Yudkin, J.: This Slimming Business, New York, 1959, The Macmillan Company, 191 pages, $3.00.

Announcement

American Therapeutic Society

61st Annual Meeting, Barcelona Hotel, Miami Beach, Florida, June 10 and 11, 1960

Preliminary program

Friday, June 10

9:00 A.M. - 12:30 P.M.	Hypocholesterolemic Agents, Chelating Agents, and Steroids
2:00 P.M. - 5:30 P.M.	Symposium on the Kidney, With Special Reference to the Newer Diuretic Agents and Procedures Moderator: Dr. John H. Moyer

Saturday, June 11

9:00 A.M. - 9:40 A.M.	Lewis Harvie Taylor Lecture
9:40 A.M. - 10:40 A.M.	Symposium on the Management of Liver Diseases Moderator: Dr. Hugh Butt
11:00 A.M. - 12:30 P.M.	Papers on Newer Drugs and Procedures
2:00 P.M. - 5:00 P.M.	Symposium on the Therapeutic Effects of Cold in Congestive Failure, Brain Injury, Myocardial Infarction, and Surgery Moderator: Dr. William Sealy